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TILT PHLEBOGRAPHY OF NORMAL LEGS

by

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DOHN (1952) described a new phlebographic technique which possesses essential advantages above previous methods. By a modification of this technique, the present author (1955, 1958) succeeded in obtaining reliable information concerning incompetent communicating veins, a matter of considerable interest from the surgical viewpoint. The procedure enables the valvular function in the deep veins to be assessed better than by previous methods and furnishes an impression of the functional capacity of the venous pump of the lower limbs. No results of the examination of normal legs by the tilt phlebography methods have so far been reported and, since a knowledge of a diagnostic method in normal subjects is of obvious importance in assessing the results likely to be obtained in disease, it seemed justified to report the experience gained in a series of normal legs, even though it comprises only 27 subjects.

It must be borne in mind that in general the method used fills superficial and communicating veins only in the presence of defective function of the valves in the communicators; other methods have to be utilized for gleaning data regarding normal communicators and the normal superficial venous system.

All the subjects were men, ranging in age from 21 to 30 years. It was ascertained that none of them had had leg complaints and that their

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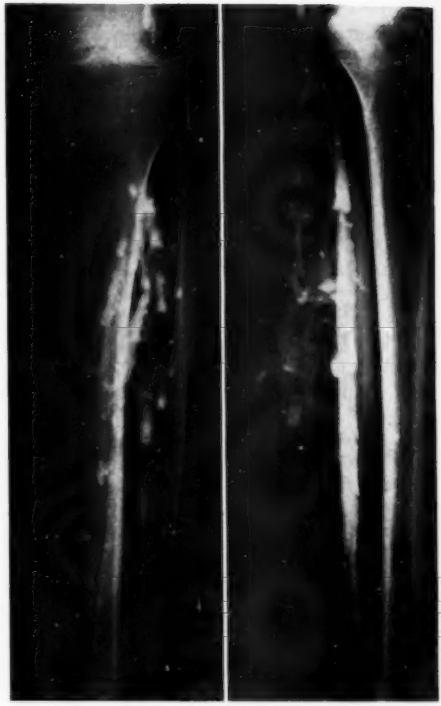
parents or siblings had not been treated for varicose disease. (The mother of one subject was suffering from mild, untreated varicosities.) There were no signs of varicose veins, eczema, ulcers, or oedema of the legs of the subjects, and in those cases in which the superficial veins were visible, the Trendelenburg test proved negative.

The technique of tilt phlebography has been described in detail by the author (1958). The only difference in this material was that a few of the examinations were performed without a tourniquet in the groin, as there was no need to fear blurring of the films due to retrograde filling of the great saphenous vein. The reading of the roentgenograms was also based upon the principles described in the above-mentioned paper. All the examinations were carried out in 1954, *i. e.* at a time when experience from about 400 tilt phlebographies of varicose cases had accumulated; in all 27 cases there was satisfactory filling of the posterior tibial vein, the fibular vein, the popliteal veins, and the superficial femoral vein.



a b

Fig. 1. Tilt phlebography of normal lower limb.
a) A. p. view: well-marked segmentation indicating closed valves.
b) Lateral view: single, well-marked anastomosis in upper part of leg and filling of a few large muscular veins despite competent valves (presumably filled during injection in the horizontal position).

Fig. 1 shows a tilt phlebogram of the lower leg of one of the subjects. The veins may be seen, with the characteristic segmentation of the contrast medium, sharply demarcated inferiorly at the sites of the closed valves beyond which the blood column is unmixed with contrast medium. Proximally, the contrast medium gradually disappears as it approaches the contrast-free blood column beyond the overlying valves. This film leaves no doubt that the valves must be competent, *i. e.* they prevent any form of retrograde filling under the conditions of the study. The same valvular pattern was found in the lower legs of all the 27 subjects (Table 1).

Table 1

State of valves in deep veins of 27 normal subjects

Valvular pattern in thigh:		
good	25	(93 %)
faint	2	
absent	0	
Valvular pattern in lower leg:		
good	27	(100 %)
faint	0	
absent	0	
Incompetent communicating veins in thigh	0	
Incompetent communicating veins in lower leg (small)	3	(11 %)
Filling of anterior tibial vein	15	(59 %)

The study thus confirmed the theoretical considerations and experimental investigations on which the method is based (DOHN 1958, MATHIESEN 1955).

Owing to the small number of subjects, the results per se probably do not rule out the possibility that absence of valvular pattern may occur in tilt phlebography of normal subjects. It is the author's experience from 700 phlebographies of patients suffering from primary varicose veins, however, that absence of valvular pattern in the lower legs is restricted to cases with a definite history of deep thrombosis. Even in the few cases in which the patients had moved the leg during the exposure, there was some trace, however indistinct, of valvular pattern. Thus, if the tilt phlebograms of the lower leg do not show definite signs of valves, this is an indication for (1) exploring the history further, and (2) making sure that the technique has been correct.

The pattern of the valves in the thigh was also sharp in 24 subjects (93 %), whereas the segmentation was less sharp in 3. Although the individual valves of the femoral vein could be accurately defined, the area below the valves was not entirely free from contrast medium. This need not, however, indicate deficient functional capacity of the valves. It may be due merely to the fact that the centrally directed blood stream has already started at the moment of exposure (DOHN 1958).

The pairs of valves visible in the thigh were counted and were found to vary in number between 2 and 7, averaging 4.2 between the groin and the popliteal in each thigh; GREITZ, using ascending phlebography, found an average of 5 pairs in the thigh. The number of valves would from anatomical studies be expected to be dependent on age, since their number decreases throughout life. This does not, however, justify conclusions

Table 2

Filling and dilatation of muscular veins of 27 normal subjects

Retrograde filling of muscular veins in lower leg	11	(41 %)
(Number showing dilatation)	(5)	
Arcade anastomoses in thigh	10	(37 %)
Arcade anastomoses in lower leg	9	(33 %)
Muscular collaterals in thigh	0	
Muscular collaterals in lower leg (only one)	1	(?)
Dilatation of deep veins in lower leg: Marked 4 / Slight 4 total	8	(30 %)

regarding pathologic conditions in the venous system concerned (RAIVIO 1948, and others).

The main object of the method is to demonstrate incompetent communicating veins. In 3 out of the 27 subjects, there was one incompetent communicating vein, medially on the lower leg, about 25 cm below the knee. This corresponds to the middle one of the three so-called juxtamalleolar communicators. This is the very communicator which is most frequently incompetent in varicose conditions (SHERMAN 1949, COCKETT 1955, and others). In all three cases, however, the communicating veins were of very small calibre, and there were no phlebographic signs of varicose veins at this or other sites of the leg.

It might perhaps have been expected that the valves of the communicating veins were competent in 'normal' subjects (*i. e.* in those without demonstrable varicose veins or varicose symptoms). Misinterpretation of the films appears very unlikely and can hardly explain the finding of incompetent communicating veins in normal cases. BERNTSEN (1925) found incompetence of communicating veins in normal subjects by injection experiments performed post mortem. RAIVIO, in his anatomical studies, also showed that valves were absent in 25 % of the cases. In his pressure measurements, HØJENSGAARD was unable to demonstrate any influence upon the pressure during walking in cases with a single incompetent communicating vein in the leg, so this defect need not necessarily give rise to symptoms. On the other hand, there is the clinical experience of the significance of communicating veins, advanced first by MORO (1910), emphasized with great force in the case of the juxtamalleolar communicators by HOMANS (1917), and recently by COCKETT (1955) inter alios.

In the three cases mentioned above, there was a question of only quite

small communicators, *i. e.* only a very slight defect in the venous pump of the calf. It is likely, therefore, that the function of the calf pump is good enough to compensate for a minor defect. In a varicose patient with secondary cutaneous changes, the same defect might be, so to speak, the last straw.

According to the result of the present study, demonstration of incompetent communicating veins does not per se appear to justify a diagnosis of varicosities.

The investigation also revealed a few points of interest with regard to the condition of the deep veins. HØJENSGAARD (1951), GREITZ (1955), and most other workers on phlebography have been concerned mainly with the filling of the muscular veins, *i. e.* the deep veins except for the tibial and fibular veins, and the popliteal and femoral veins, under one heading. On the basis of the experience, partly from this normal series and partly from a series of 1,200 investigations of patients with various venous abnormalities, the author has attempted a more detailed description of the filling of the muscular veins seen in the lower leg (and in some cases in the thigh as well):

1. The sural veins and the soleal muscle veins form a natural unity in the phlebograms showing the above-mentioned muscular filling, and have a characteristic oblique course, upwards and forwards. They may be seen closely behind the posterior tibial vein (soleal muscle veins) or in the upper third of the calf (sural veins).

2. In some cases arched well-marked anastomosing coils are evident in other sites in the lower half of the calf. Merely the way in which they show up in the phlebograms make it reasonable to assume that these must be anatomic variations within the range of normal.

3. Finally, there may be filling of a fine-calibred, mainly longitudinal net in the muscles, designated as 'muscular collaterals'. These muscular collaterals may be apparent throughout the muscles of the calf, *i. e.* at the site of the soleal muscle veins as well as more posteriorly and inferiorly. A similar venous pattern may be seen posteriorly in the thigh, and as a rule these collaterals present a characteristic picture, entirely different from the above-mentioned anastomoses, being both more numerous and of finer calibre.

Filling of the muscles of the calf was evident in 20 out of the 27 subjects (74 %). This percentage is a little higher than HØJENSGAARD's in varicose patients. Since, however, the diagnostic techniques were entirely different, the two series are not comparable.

Classification of the findings into the 3 above-mentioned groups (Table 2) showed so-called retrograde filling of muscular veins of the leg (Group 1) in 11. In 5 of these cases the filled veins must be regarded as dilated. There was an unmistakable pattern of valves in the muscular veins of all subjects, but not always at their junction with the tibial or fibular vein. A single, large, arcuate or transverse, deep anastomosis in the leg (Group 2) was seen in 9 subjects (33 %). The anastomoses frequently arose from the lower part of the posterior tibial vein or the fibular vein and ended as a muscular vein in the soleal group. Fig. 1 b gives an example of such an anastomosis. Similar anastomoses were present in the thigh between the superficial femoral vein or the popliteal vein and the deep femoral vein in ten subjects (Fig. 2 a).

a b

Fig. 2. Tilt phlebograms.

a) Normal thigh, showing anastomosis between the superficial and the deep femoral vein.

b) Normal lower leg (lateral). Inferiorly, an arched anastomosis between the posterior tibial vein and the fibular vein; superiorly, an anastomosis (or possibly a solitary muscular collateral) from the posterior tibial vein to the sural veins.

Typical examples of 'muscular collaterals' were not observed among these 27 normal cases. One had a single, relatively fine-calibred longitudinal vein posteriorly in the muscular tissue of the leg. This phlebogram is shown in Fig. 2 b. Inferiorly there is a typical, arched anastomosis, and proximally the pattern also suggests an anastomosis. In Table 2, however, the latter is classified as a possible muscular collateral. Spindle-shaped dilatation, as reported by HØJENSGAARD 1951, HENDRICHSEN 1951, GREITZ 1955, and others, was observed in several cases.

In other words, the present study showed that a number of phlebographic findings previously considered pathologic are also demonstrable in normal subjects, using the word 'normal' in its widest sense. Several of these findings are merely a confirmation of previous investigations.

Incompetence of communicating veins has not, however, previously been demonstrated in normal cases by a method which permits a definite diagnosis of the incompetence. As emphasized above, the fact that incompetence has been demonstrated in normal subjects probably does not mean that these changes are of no pathogenic significance. On account of the youth of the subjects, a similar reserve must be made in assessing the other phlebographic findings in the absence of information regarding a possible predisposing cause of the subsequent development of varicose veins (or some other venous disorder). It is worth mentioning, however, that the muscular collaterals were not definitely demonstrable.

SUMMARY

Twenty-seven legs of normal, healthy men were examined by tilt phlebography. The different phlebographic findings in 'normals' do not definitely rule out any pathogenic significance. There was only one case of 'muscular collaterals' and the incompetent communicators demonstrated were solitary and small. Well-marked valves were demonstrated in the fibular and posterior tibial vein in all the subjects.

ZUSAMMENFASSUNG

Die unteren Extremitäten 27 normaler gesunder Männer wurden mit der Wippenphlebographie untersucht. Die verschiedenen phlebographischen Befunde bei 'Normalen' ergeben keine definitive pathogenetische Signifikanz. Nur in einem Falle lagen 'muskuläre Kollateralen' vor und die nachgewiesenen inkompetenten Kommunikanten waren solitär und klein. Gutmarkierte Klappen wurden bei allen Personen in der Vena fibularis und in der Vena tibialis posterior nachgewiesen.

RÉSUMÉ

L'auteur a examiné par phlébographie basculante vingt-sept membres inférieurs d'hommes normaux, en bonne santé. Certains aspects phlébographiques trouvés chez des sujets 'normaux' ne sont pas absolument dénus de signification pathologique. Il n'y a eu qu'un cas de 'collatérales musculaires' et les communicantes insuffisantes mises en évidence étaient isolées et petites. Des valvules bien marquées ont été mises en évidence sur les veines péronière et tibiale postérieure de tous les sujets.

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THE VALUE OF INTRAOSSEOUS VENOGRAPHY IN TUMORS OF THE FEMALE PELVIS

by

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In previous publications, we have discussed the use of the intraosseous venography and the roentgenographic findings in involvement of the azygos vein in diseases of the chest and the mediastinum, of the vertebral plexus in lesions of the spine and in pathologic conditions of smaller bones.

This paper is published to report about our experience with the intraosseous venography, a method of examination indicating diseases of the female pelvis. The objective of the investigation was:

1. To localize lymph node involvement in early carcinoma of the cervix.

2. To locate recurrence of any tumor tissue, and thereby to advance early detection of recurrence by control roentgenography.

Our results are based on the evaluation of 71 cases (with bilateral intraosseous injection into the greater trochanter area).

We have previously discussed some of the physiological aspects and the anatomy of the vertebral venous system. Since the work of BATSON, we know how important the venous channels are in the development of

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metastases, especially of tumors in the pelvis. A preliminary review of the topographic anatomy of the venous circulation related to the area under discussion will be given.

Outside the vertebral column, a venous network is distributed as an anterior plexus in front of the vertebrae, and a posterior plexus around the spinous process. These two plexuses communicate freely with each other and over the lower part of the vertebral column they are linked by the ascending lumbar veins, one on each side. These latter are connected with the common or internal iliac veins and the presacral plexus of veins, including the middle sacral vein, at their lower ends, and ascend to become the azygos vein (on the right) and the hemiazygos vein (on the left). The external vertebral plexus, which drains ultimately into the superior vena cava, also anastomoses freely with the internal vertebral plexus, which lies within the vertebral canal between the dura mater and the vertebrae and receives tributaries from the bones and the spinal cord. The plexus extends the whole length of the canal and communicates directly or indirectly with various veins of the trunk, arms, head and neck. The main links between the internal and external vertebral plexus are the intervertebral veins which pass through the intervertebral foramina. Although the whole of this venous system is subject to many variations in detail, it is fairly constant so far as the essential features are concerned and it does provide a theoretical pathway from the pelvis to other parts of the body which is not interrupted by the lungs. Its existence has long been recognized, but during the last 100 years interest in it has centered mainly on its function as a collateral pathway for blood from the pelvis and legs when the inferior vena cava becomes obstructed by disease or by operation. It is now generally accepted that the lumbar veins serve as one of the main routes for blood when the inferior vena cava is obstructed either in man or animals. Any argument which remains is concerned with their function when the caval circulation is intact.

Nevertheless, so far as we know, the actual passage of blood and other material from the uterus to the vertebral plexus in a live woman with a normal circulation was first reported by JEFFCOATE and it was the result of its incidental observance during a hysterosalpingography.

The experience goes to substantiate the probability of this route being sometimes used for the spread of tissue cells, blood clots and organisms from the pelvis to remote parts of the body.

It is apparent that the vertebral plexus system is a valveless complex set of veins, lying outside the thoracic and abdominal cavities, not subjected to direct pressure of the thoracic and abdominal cavities.

In contradistinction to this, the abdominal pressure in this study of the parietal pelvic-venous system plays an important role which has to be considered.

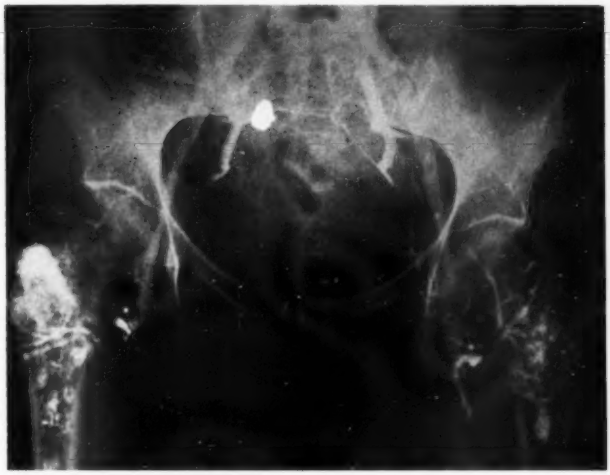

Fig. 1. Early contrast-filling of the parietal-pelvic-venous system after injection of 12 ml Hypaque into the greater trochanters.

Although the anatomy of the parietal pelvic-venous system is well known, the exact knowledge concerning the flow of the blood from the visceral to the parietal veins and vice versa is not yet well understood. Also the different pathways of the venous flow to the hypogastric system are still problematic under certain pathological circumstances and they are dependent on factors which are subjected to further investigation.

The studies of DUCUING and of BAUX in 1950 have shown by experience that there are certain areas of choice for the injections of the contrast medium. As we now know from our studies and from other investigators, only the parietal venous system is demonstrated by this method as the visceral system can only be demonstrated in direct approach. To refer to the main points of injection in the pelvis, four regions were found most suitable:

1. The os pubis which, after injection of contrast medium, drains into the obturator veins or obturator plexus with contrast-filling of the hypogastric vein.

2. Injection into the ischial bone is followed by drainage into the ischial vein with demonstration of the obturator veins, plexus and the hypogastric vein.

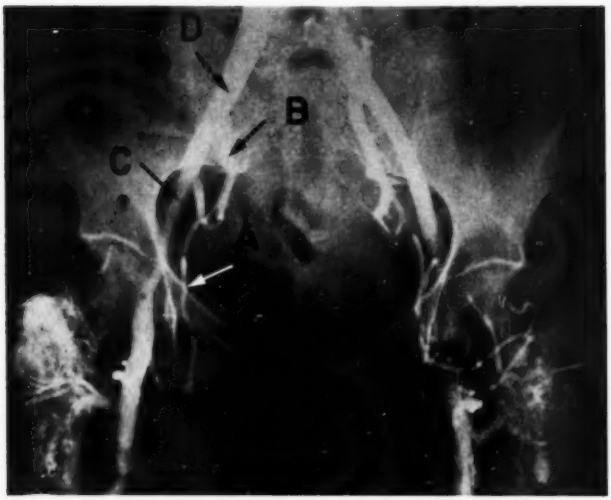

Fig. 2. Complete contrast-filling of normal parietal pelvic-venous system after injection of 25 ml Hypaque into the greater trochanters. A — obturator, B — hypogastric, C — external iliac, and D — common iliac, veins. Femoral, circumflex, and inferior vena caval veins also demonstrated.

3. Injection into the iliac crest shows the hypogastric vein which is usually filled by an innominate vessel, which seems to be intraosseous in localization, and by some gluteal veins.

4. Injection into the greater trochanter results in demonstration of the hypogastric vein, external iliac vein, filling of the obturator plexus through the circumflex femoral vein and also in most of the cases the deeper femoral vein.

In our studies, the bilateral injection into the greater trochanter was the area of choice. Hereby we were able to obtain the most complete contrast-filling of the parietal pelvic-venous system. Since we have taken serial films manually, we obtained an early partial filling and a late complete filling of the venous channels (Fig. 1). As we had thought, pelvic disease produced either obstruction or displacement of venous channels. Sometimes also vascularization of tumor masses along the course of the venous channels could be observed. The large lymph nodes in the true pelvis are most likely found at the level of the larger vessels, especially in the hypogastric, external iliac and also the obturator area. Evaluation of this venous system with its ramification was of greatest interest for our examination.

Fig. 3. Displacement of proximal portion of right hypogastric vein with delayed contrast-filling. Slight compression of right external iliac vein. Metastatic lateral pelvic disease on the right side suggested. (Clinical diagnosis: carcinoma of cervix, Stage I. Cervix extensively ulcerated. No lateral pelvic disease. At surgery: large lymph nodes at the level of the bifurcation of right external iliac and right hypogastric veins.)

It is known that the distribution of the larger and medium-sized venous channels in the pelvis is looser and less regularly arranged in its course; therefore the evaluation of the roentgen findings has to be very careful with respect to the appearance and recognition of the variety of these venous channels.

It is also important to realize that the obturator veins may be present, single or double, with their superior branch draining to the external iliac, the inferior branch draining to the hypogastric. If only a single one is present, it usually drains to the hypogastric vein. We must also keep in mind that the ischial vein, more of extrapelvic origin, is of special value in the contrast-filling of the hypogastric veins. The anastomoses of the pelvic veins are abundant and multiple, varying in almost every person to a greater or lesser degree. They help to form the visceral and parietal system of venous channels. Also the presence of valves in the greater veins have to be considered, since it has been found, for example, that the valves of the hypogastric veins hinder the reflux of the venous blood from the parietal into the visceral system. On the other hand, the hypogastric veins are connected with the presacral venous system which lies in close connection to the sacral vertebral plexus.

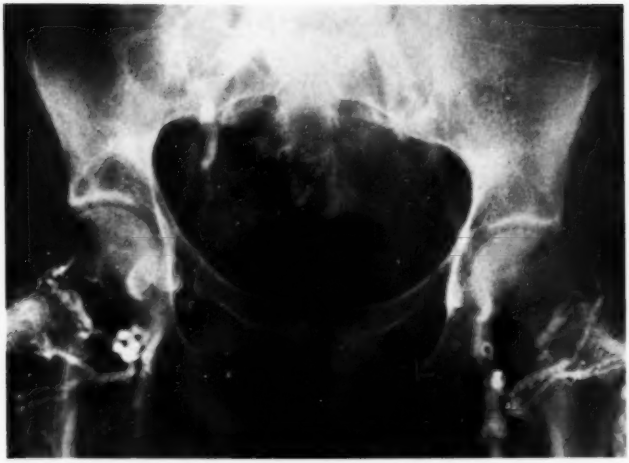

Fig. 4. No contrast-filling of left obturator vein, displacement and incomplete filling of left hypogastric vein. Metastatic disease of left lateral pelvic wall. (Clinical diagnosis: carcinoma of cervix, Stage I, with questionable involvement of left pelvic lymph nodes. At surgery: metastatic involvement of lymph nodes invading left obturator and left hypogastric veins.)

Comparing the right side of the venous channel with the left, we have to be aware that, on the left side, the flow of the contrast medium in the venous system is more complicated than that of the right side. After the injection of contrast medium, the flow of the right side is simple and direct. Filling of the obturator and hypogastric veins or plexus is noted and the blood drains into the external iliac and to the inferior vena cava. In some instances the presacral plexus is demonstrated.

On the left side, however, after contrast-filling of the obturator and the hypogastric veins, the venous blood usually flows directly to the presacral plexus which functions from the left to the right side also. The external iliac is usually filled and demonstrated by the flow of the contrast medium through the circumflex femoral through the lower portion of the pelvis by the femoral vein. After filling of the presacral area, the drainage from the hypogastric passes into the external iliac. Furthermore, it has to be considered that due to the topographic anatomical relation between the external and common iliac veins to the external and common iliac artery to the pelvic wall, on the left side the flow of the venous blood is somewhat delayed as compared to the right side, which is explained by hydraulic phenomena.

Without going into further detail, these are some of the facts which have to be contemplated in the evaluation of the radiologic findings.

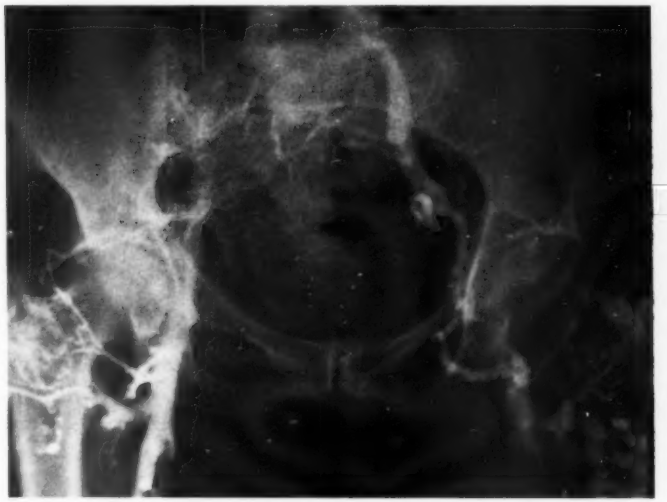

Fig. 5. Large tumor mass, vascularized. Obstruction of right hypogastric and right obturator veins. Displacement of right external iliac vein. (Clinical diagnosis: carcinoma of cervix, Stage II, with pelvic nodes anterior and posterior to the pelvic wall. Autopsy: Large tumor mass in right pelvis invading the large pelvic veins.)

Technique

The procedure, which is relatively simple, is carried out in the following manner. An ordinary bone marrow set with two Lundy-Irving needles, size 16, (about 7.6 cm) and four syringes of 2 ml, 10 ml, 20 ml and 25 ml size are utilized. Before the study is undertaken, the usual precautions are observed in regard to possible allergy to iodine. The patient is sedated with seconal, morphine and scopolamine about 1 1/2 hours before the examination. A dose of morphine (1/4 grain) and scopolamine (200 mg) is again given 45 minutes before the study so that the patient comes to the examining table under a heavy sedation as in 'twilight sleep'. After local anesthesia of both sides of the femora in the areas of the greater trochanters with 1% procaine has been carried out, the bone marrow needles are introduced down to the periosteum.

When the bone marrow needle is felt to be securely in place in the medullary cavity, an aspiration is carried out and the presence of a small amount of bone marrow aspirate proves that the needle is in correct position. To insure adequate localization of the needle, a preliminary film is obtained after the injection of 1 or 2 ml of contrast medium. Then bilateral injection of 25 ml of Hypaque 50 % is carried out simultaneously.

Fig. 6. No demonstration of right hypogastric and obturator veins. Slight lateral displacement of right external iliac vein. Metastatic lymph node involvement on the right side suggested. (Clinical diagnosis: recurrent carcinoma of cervix, Stage V, with right pelvic mass and nodes. At surgery: large metastatic lymph nodes invading right hypogastric, obturator and external iliac veins.)

Although the contrast medium is cleared rapidly from the site of injections, manual exchange of films will allow 3 to 4 films to be obtained. In this investigation, no automatic rapid cassette changer was used. The first film is taken after about 12 ml have been injected bilaterally, the second film after 25 ml, and one or two films after the injection is completed. Follow-up films made 6 to 8 hours later show no evidence of contrast medium at the site of injection.

Histological and toxicity control of intraosseous venography. In the experimental work of WILD, contrast medium was injected into the bone marrow of dogs. It has been shown that the injection of contrast medium into the same area on two different occasions was not followed by the appearance of pathologic findings. However, more frequent injections into the same region resulted in local inflammatory reactions. The trabecular architecture of the bone marrow may show changes in structure which, though they heal spontaneously, may last for a long time. Other organs were not found to show any side effects. Complications, such as thrombophlebitis, delayed hemorrhage, fever and local reactions, as observed by LESTER and LAMPE, and HILSCHER in their studies in human beings have not been encountered in any of our examinations. But we have to mention that the patients complained of pain after the injection. Pain is usually noted during the injection and a short while after the

Fig. 7. Lateral position of right hypogastric vein and proximal part of right obturator vein. (Clinical diagnosis: carcinoma of cervix, Stage I. No evidence of lateral pelvic disease. At surgery: no pelvic pathology except for an abnormal course of right hypogastric and proximal portion of right obturator vein.)

injection has been carried out. Though the intraosseous venography is a convenient method of examining these particular vascular channels, it has, however, its risk for the patient and certainly there are contra-indications to this procedure. Oversensitivity to anesthesia or to the contrast medium may be of considerable danger to the patient. Acute pelvic inflammatory conditions are still considered, in many places, to be absolute contra-indications. In general, advanced age does not represent a contra-indication to this method.

Discussion

The diagnostic value of intraosseous venography in tumors of the female pelvis will now be discussed. It seems adequate to classify the study in two categories.

1. Carcinoma of the cervix, Stages I to V, 47 patients, which also include 4 cases of secondary metastases to the gyntract involving the tubes, broad ligaments and pelvic wall.

Fig. 8. Tortuosity and narrowing of the caliber of the pelvic veins with stasis and delayed filling of the common ilial veins. (Clinical diagnosis: recurrent carcinoma of the pelvis, Stage IV, after irradiation with the clinical findings of a 'frozen' pelvis. At surgery: no evidence of recurrent disease in the pelvis. Bilateral fibrosis and adhesions.)

2. Involvement of the pelvis by diseases other than carcinoma of the cervix, 24 patients.

These cases were studied by the radiologist without knowledge of the clinical pelvic findings of the gynecologic examiner.

Seventy-one cases were examined of which 4 were technically unsatisfactory.

Category 1. Eighteen cases of carcinoma of Stages II to V were studied and in all of them marked pathological changes in the course and distribution of the venous channels were demonstrated. The most frequent alterations were obstruction of some venous channels, stasis of the contrast medium in the involved side associated with the formation of collaterals.

A less frequent finding was displacement of the venous channels with stasis and the presence of collaterals.

As a rare finding, tumor vascularization in addition to obstruction and stasis was encountered (Fig. 5).

The findings obtained in the aforementioned cases of secondary metastases to the gyntract were identical with those of primary cervix involvement.

In 14 of 22 cases of the first category, the surgical or post-mortem findings were in complete agreement with the radiological impression, and showed the presence of tumor masses and nodes in the pelvis obstruct-

ing the venous channels by direct invasion or extrinsic compression. The remaining 8 cases are still being treated for recurrent pelvic disease and no surgery has been done.

Twenty-five cases of carcinoma of the cervix, Stage I, were examined. In 23 patients, there was complete agreement between the gynecologist and radiologist that no lateral pelvic disease was present. One case revealed, on clinical examination, a normal pelvis which did not agree with the radiologic findings which consisted of displacement and stasis of the right hypogastric vein thought to be due to large metastatic nodes. This was confirmed by surgery. In the other case the right hypogastric vein had an abnormal course which was found to be lateral to the external iliac vein. The clinical examination of this patient did not reveal any pathologic changes in the pelvis on the right side. At surgery only a variation in the formation of the right hypogastric vein was found. Twenty-four of the 25 patients of this group are still being followed for 12 to 24 months after treatment and have been found free of recurrent disease. One woman died from a cause other than pelvic disease and on autopsy the pelvis was found to be free of tumor.

Category 2. This group of patients with diseases involving the gyn-tract other than carcinoma of the cervix comprises cases with the following lesions or pathologic conditions: 6 adenocarcinoma and sarcoma of the uterus, 2 fibroid uterus, 2 endometriosis, 2 carcinoma of the vulva, 3 carcinoma of the ovaries, 2 with inflammatory condition of the female pelvis, 6 with 'frozen' pelvis after irradiation, and 1 case of tubal pregnancy.

In this category, in which 4 cases were technically unsatisfactory, the radiological examination with intraosseous venography did not show any pathological or revealing findings with the exception of the cases with the 'frozen' pelvis. Here the vascular pattern displays irregularities and tortuosity with narrowing of the caliber of the pelvic venous vessels. Occasionally these findings were also associated with the presence of smaller collaterals and with delayed filling of the iliac veins (Fig. 8).

Other investigators such as BAUX, DUCUING, GUILHEM, have suggested the bilateral intraosseous injection into the pubic or iliac bones, into the iliac crest or the greater trochanter of the femora.

We have found that the bilateral trochanteric injection is the method of choice for the best demonstration of the parietal-pelvic-venous system. It is important to perform the procedure with serial films taken during the injection. In this manner we are able to record the different phases of the filling of the pelvic-venous system. It is our impression that only the early filling of the venous channels gives information concerning the pathway of the collaterals, whereas the later films reveal the morphologi-

cal changes of the venous channels and their course. Based on this study we believe the intraosseous venography is of value in cases of carcinoma of the cervix and in metastatic involvement of the female pelvis. No reliable information can be obtained in the group of diseases which we discussed in the second category, except in the cases of frozen pelvis in which an abnormal, but not typical, pattern of the pelvic veins may be found.

Acknowledgement

We are indebted to Dr. James Palmer for the referral of patients, for his stimulating interest and fruitful discussions.

SUMMARY

A radiologic investigation was made to localize lymph node involvement in early carcinoma of the cervix and to locate recurrence of tumor tissue by intraosseous venography. A short description of the technique and its side effects is given on the basis of a material of 71 cases and the pathologic findings of the parietal pelvic venous system are discussed. Intraosseous venography is of value in the detection of pelvic lymph node involvement in patients with carcinoma of the cervix.

ZUSAMMENFASSUNG

Eine röntgenologische Untersuchung mit intraossöser Venographie ist ausgeführt worden, um Lymphknoteninfiltrate beim frühen Cervixkarzinom zu lokalisieren und um Tumorrezidive festzustellen. Die Technik und ihre Nebenwirkungen werden unter Bezugnahme auf ein Material von 71 Fällen kurz beschrieben und die pathologischen Befunde im parietalen Beckenvenensystem werden besprochen. Die intraossöse Venographie ist für die Entdeckung von Metastasen in Beckenlymphknoten bei Patienten mit Cervixkarzinomen wertvoll.

RÉSUMÉ

Les auteurs ont fait un travail de recherche radiologique pour localiser l'atteinte des ganglions lymphatiques dans le cancer du col de l'utérus au début et pour localiser les récidives de tissu tumoral, par phlébographie intra-osseuse. Ils décrivent brièvement, d'après une série de 71 cas, leur technique et ses incidents et étudient les modifications pathologiques du système veineux pariétal pelvien. La phlébographie intra-osseuse est utile pour déceler l'atteinte des ganglions lymphatiques pelviens chez les malades atteintes de cancer du col.

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CLEIDOCRANIAL DYSOSTOSIS

Report of two cases with special characteristics

by

Johannes Thoms

Cleidocranial dysostosis is due to deficient or delayed development of the bones preformed in connective tissue or cartilage. Deficient ossification of the bones preformed in connective tissue gives rise to the most characteristic manifestation of the condition, viz. large cranial defects and defective development or complete absence of the clavicles. However, disturbances in the ossification of the bones preformed in cartilage also often result in considerable anomalies, for example, of the spine, pelvis, hips and phalanges. Wide variations in both extent and degree of the abnormalities have been reported. For systematic descriptions of the condition, the reader is referred to the exhaustive surveys by FAIRBANK, ZELWEGER, ELTORM, inter alios.

OLLERENSHAW (1938) reported two cases in a brother and sister with calcifications in the skin and soft parts, while THOMSEN and GUTTADAURO (1952) seem to be the first who have described osteo-sclerosis as a complicating sign or accompanying manifestation. The bone fragility resulting from the sclerosis is of crucial importance in the degree of disability

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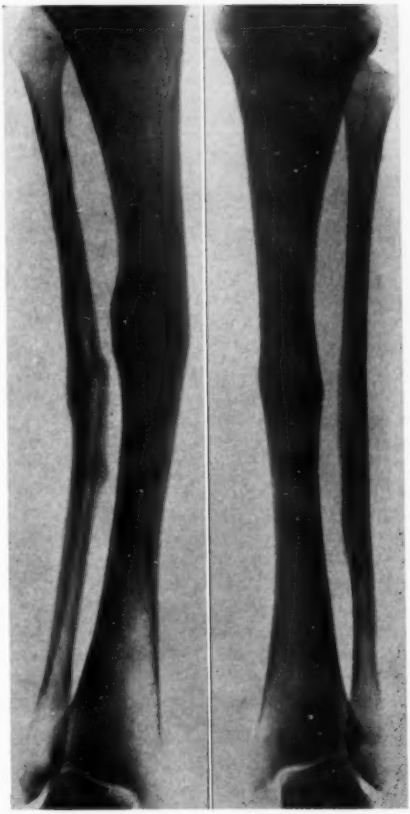

b c

Fig. 1. Case 1.

a) Lateral view of spine showing the canals in the vertebral bodies for the basivertebral veins.
b) and c) Roentgenograms of lower leg. Osteosclerosis and almost identical sequelae of fractures present.

of the patients. As the disease is rare, two cases which have been seen in this hospital are reported below.

The external appearance of the subjects is characteristic. They are small individuals with plump limbs but a slender trunk. The hands and fingers are short and broad. The shoulders are narrow and drooping, with a tendency to winged scapulae and the lumbar lordosis is accentuated. The skull is square with prominent frontal and parietal tubera, and the temporal regions are sunken. The thick, slightly pendulous cheeks and the underdeveloped chin contribute to the squarish configuration of the head. The teeth of the lower jaw show some protrusion due to hypoplasia of the facial bones.

Case reports

Case 1. Woman, aged 28, youngest of 14 children. A brother and sister (the 4th and 5th of the sibship) also suffered from cleidocranial dysostosis. The parents were in good health; no other known cases of cleidocranial dysostosis, dwarfism, or proneness to fractures in the family. As a child the patient had sustained a number of fractures, caused by slight or moderate traumata. During the last few years she easily became tired and there was a tendency to pain and muscular weakness in the back and limbs. Mentally retarded, marked dwarfism, height 134 cm, bodyweight 41 kg. Otherwise nothing abnormal on physical examination. No abnormal laboratory findings.

The patient's brother is identical with Case 2 reported by THOMSEN and GUTTADAURO. With regard to physical and mental development, this brother and another sister presented exactly the same conditions as those in the case now described.

Roentgenologic findings. There were considerable defects in the cranial bones, with widely separated sutures (up to 3 cm) and some irregular Wormian bones in the parietal regions. There was slight asymmetry of the skull, so that the margins of the right and left parietal bones did not form a regular surface. The sella turcica was normal. The sphenoid sinus was underdeveloped, the frontal sinuses were absent, and the ethmoid cells and maxillary sinuses were very small. The maxillae were small and hypoplastic. The angle of the mandible was very wide, and the teeth of the lower jaw showed some protrusion. Caries and paradentosis were present.

The clavicles were rather short and there was slight hypoplasia of the acromial ends. The vertebral margins of the scapulae lay outside the lateral contour of the thorax, suggestive of winged scapulae. A horizontal, central defect in most of the vertebrae extended from the anterior margin to the middle of the bodies. The spinous process of the twelfth thoracic vertebra was very small, irregular, and hypoplastic.

Almost complete absence of the unguicular tuberosities of both hands was noted and the terminal phalanges were hypoplastic and tapered. Pelvis and hip regions: bilateral coxa valga, no signs of delayed osseous development. Sequelae of tibial fractures with smooth callus formation were noted on the two sides. The left fibula had also been fractured.

The skeletal system as a whole showed diffuse osteosclerosis. The substantia compacta of the long bones was considerably thickened and the sclerosis involved the base of the skull, the facial bones, and the parietal bones.

Case 2. Girl, aged 9 months, the younger of two children admitted to hospital because of failure to thrive and recurrent catarrhal attacks. Parents and brother in good health. Physical examination: Height 64 cm (normal 72 cm), bodyweight 6.6 kg (normal 9.2 kg); thoracic circumference 39 cm (normal 45 cm). No other abnormal physical signs apart from adenoids.

Roentgenologic findings. The skull had large fontanelles and widely open sutures. Wormian bones were present in the parietal regions. The mandibular angle was very wide on both sides, and the mandible and maxillae were hypoplastic. The developing dental tissue seemed normal. The osseous structure was fairly dense, especially in the parietal and frontal bones.

The medial third of the left clavicle was completely absent, and the remaining part of the left and the whole of the right clavicle were hypoplastic. The osseous structure of the spine and ribs was denser than normal. Hypoplasia of the terminal phalanges of the fingers of both hands was present. The terminal phalanges were tapered and the unguicular tuberosities undeveloped. The carpal and metacarpal bones had a dense, fairly sclerotic structure, and the cortex was thickened. Bilateral coxa valga was present, and the bone

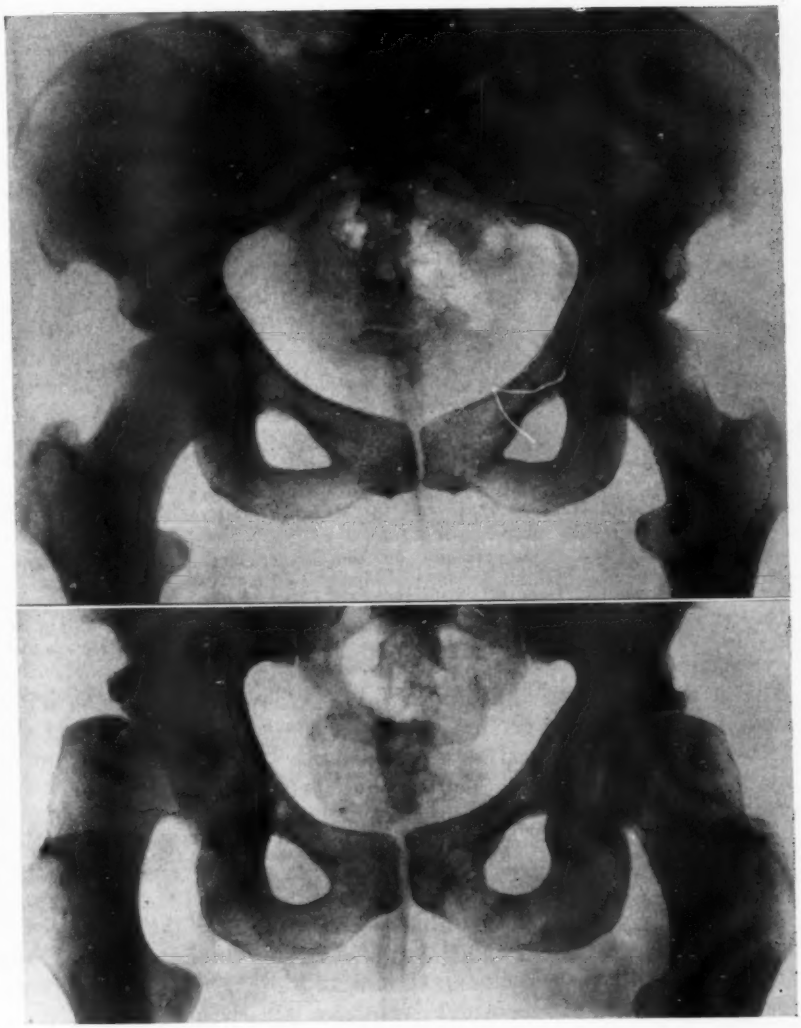

Fig. 2. A. p. views of pelvis and hip region. Varying degree of coxa valga.

density was slightly increased in the proximal part of both femora. The substantia compacta of both femoral shafts was thickened. The development of the centres of ossification was normal.

Roentgenologic examination of the first patient's brother and sister revealed conditions which were almost identical with those observed in Case 1. It may be noted

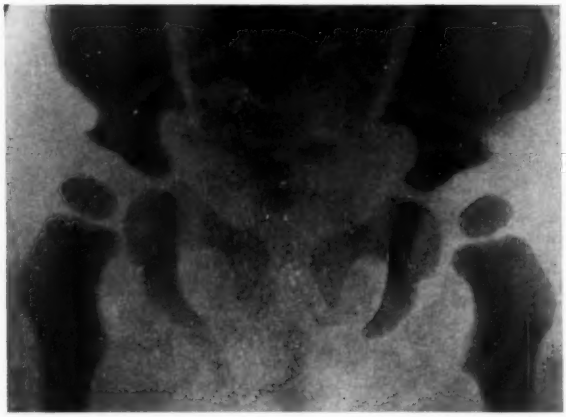

Fig. 3. Coxa valga. Case 2.

that changes in the clavicles of these patients were also minimal, and that both had bilateral coxa valga. Just as for the patient reported upon in Case 1, marked osteosclerosis of the entire skeletal system was present, and the changes in the cranial bones and the bones of the extremities, especially the phalanges, were also exactly the same.

Discussion

The patients presented a number of bone changes characteristic of cleidocranial dysostosis. Even though the clavicular changes in Case 1 and the two siblings were relatively slight, the other developmental anomalies observed were so marked and typical that the diagnosis of cleidocranial dysostosis was unquestionable. According to STOCKS and BARRINGTON, absence of the sternal end of the clavicle with preservation of the acromial end, as was found in Case 2, is the rarest anomaly of that bone.

The broad horizontal canals for the basivertebral veins visible in the vertebral bodies in Case 1 (Fig. 1 a) are worthy of note. This finding must be considered as evidence of the inhibition of osseous development, but is not typical of cleidocranial dysostosis. On the other hand, a cleft of the vertebral arch is a frequent observation, but this was absent in the cases considered here.

In previous descriptions of cleidocranial dysostosis, coxa vara is stated to be a characteristic and frequent anomaly, while coxa valga seems to have been observed only in one previously reported case (ZELWEGER et coll.). Figs. 2 and 3 show films of the pelvis and hip regions. In the adult siblings a distinctly varying degree of coxa valga is seen. In Case 2,

the angle between the neck and the shaft of the femur was 160° to 170°. Even though this patient was only 9 months old, the valgus position of the hips must be presumed to be of a permanent nature since, even when allowance is made for the age, the angle between the neck and shaft is greater than normal. None of the patients revealed definite abnormalities of the pubic or other pelvic bones.

Finally, the peculiar osteosclerosis observed in the cases is noteworthy. This and the attendant bone fragility is best illustrated by films of the lower legs of the adult patients (Fig. 1, b and c). The sclerosis and sequelae of fractures render the roentgenograms almost identical and add to our understanding of the increased degree of disability in these patients. Neither the roentgenographic appearances nor the laboratory findings offer any explanation of the osteosclerosis. As in the cases reported by THOMSEN and GUTTADAURO, it must be considered to be due to the same unknown factor as that which causes cleidocranial dysostosis.

SUMMARY

Two cases of cleidocranial dysostosis together with comparative studies in two siblings of one of the patients, are reported. Osteosclerosis was observed in all four patients and in three of them had caused an increased tendency to fractures. All the patients had bilateral coxa valga as distinct from the usual finding of coxa vara in patients with cleidocranial dysostosis. The typical appearance of the patients is described and the roentgenographic observations are discussed.

ZUSAMMENFASSUNG

Zwei Fälle mit kleidokranialer Dysostose sowie vergleichende Studien über zwei Geschwister des einen Patienten werden berichtet. Osteosklerose wurden bei allen 4 Patienten beobachtet; sie hatte bei 3 von ihnen eine erhöhte Frakturtendenz verursacht. Alle Patienten hatten doppelseitige Steilhüften an Stelle des üblichen Befundes einer Klumphüfte bei Patienten mit kleidokranialer Dysostose. Das typische Aussehen der Patienten wird beschrieben und die röntgenologischen Beobachtungen werden diskutiert.

RÉSUMÉ

L'auteur présente deux cas de dysostose cléido-cranienne, ainsi que l'étude comparative de deux parents de l'un des malades. Il a constaté une ostéoclérose chez ces quatre sujets, ayant entraîné chez trois d'entre eux une fragilité osseuse. Tous ces sujets avaient une coxa valga bilatérale, alors qu'on trouve habituellement une coxa vara chez les sujets atteints de dysostose cléido-cranienne. L'auteur décrit l'aspect typique de ces malades et analyse les signes radiographiques.

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EMPTYING OF THE HUMAN GALLBLADDER UNDER THE STIMULUS OF CHOLECYSTOKININ

by

Paul Edholm

According to IVY et coll. (1928) the action of secretin preparations on the gallbladder is due to a specific gastrointestinal hormone, cholecystokinin, which, like secretin, is derived from the duodenal mucosa. It was found that cholecystokinin, if injected intravenously, caused contraction of the gallbladder. Its value in roentgenography of the biliary system was studied by IVY et coll. (1930), IVY (1947), DENTON et coll. (1949), IVY (1955), and DUNCAN et coll. (1953).

JORPES & MUTT (1954, 1955) purified the hormone and made it available for clinical trial (WERNER et coll. 1954). It has been tested in several Swedish hospitals and the first reports on its value in the roentgen diagnosis of biliary disease were published by BRODÉN (1956), ADLERCREUTZ et coll. (1957), and JORPES et coll. (1957, 1958). It has also been tested in the Roentgendiagnostic Department of Karolinska Sjukhuset; these trials are now reported in greater detail.

Case material and Method

The patients examined numbered 102. They all presented symptoms which might have been referable to biliary disease, and had a functioning gallbladder. They were divided into the following groups, viz.: Group I — No calculi demonstrated (32 cases), and Group II — Calculi demonstrated (70 cases).

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Diagram 1. Interval between onset of drip and exposures (white arrows) and duration of drip (dark area).

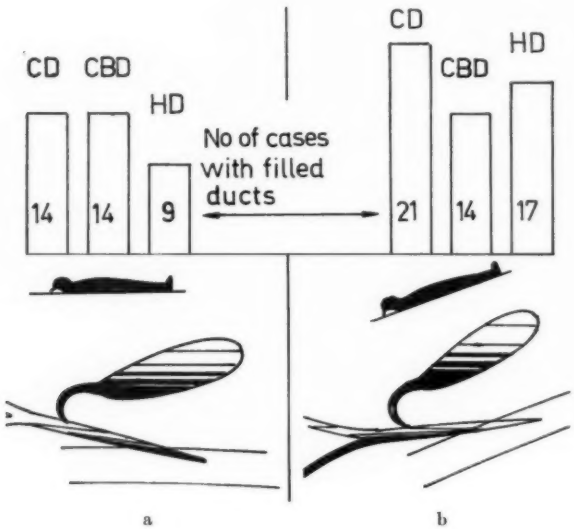

Diagram 2. Relationship between 'spontaneous' filling of bile ducts and the patient's position group II (70 cases), examined in: a) with 35 patients supine, and b) with 35 patients supine and couch inclined 15 to 20°. (Figures in columns indicate number of filled ducts.) CD — cystic duct, CBD — common bile duct, HD — hepatic duct.

With the exception of a few cases in which Bilijodon-Na was given, Telepaque was the contrast medium used. The patient was instructed to swallow the tablets on two consecutive days, 6 on the first and 9 on the second day.

Of the 102 patients in this series 5 were examined in the prone position, and 97 in the supine right anterior oblique position (15 to 20 degrees). In 59 cases the patient was examined horizontally, and in 43 the roentgen table was tilted so that the patient was head downwards. The patient being positioned, the first roentgenogram was obtained; this was viewed and cholecystokinin was given in order to empty the gallbladder. (The cholecystokinin was prepared at the Chemistry Department, Karolinska Institutet, Stockholm, and the lyophilised product was delivered in sterile ampoules. A commercial product under the trade name Cecekin Cholecystokinin Vitrum, has become available in sterile ampoules containing about 3 mg of the freeze-dried substance. It is marketed by Vitrum AB, Stockholm.)

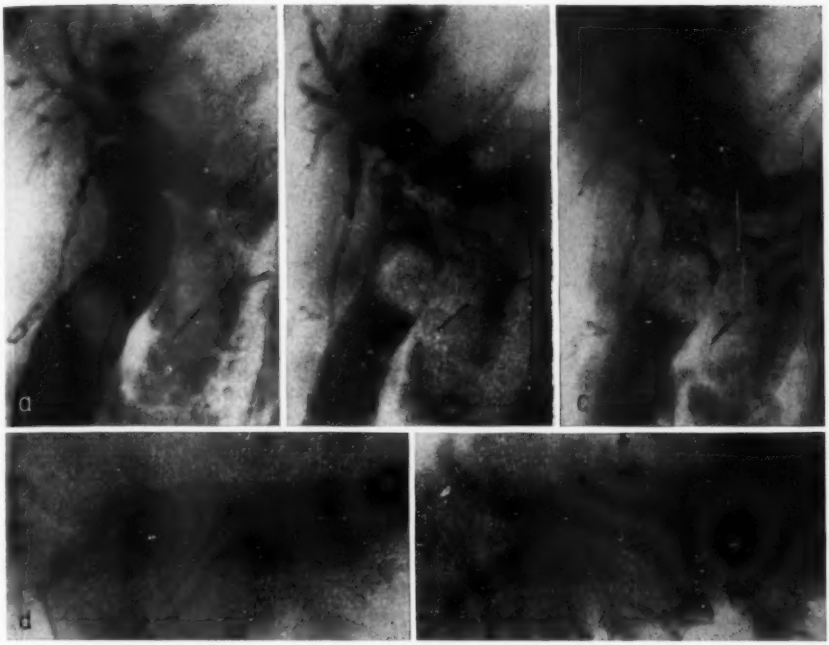

Fig. 1. Gallstones. Patient tilted head downwards. A.p. roentgenograms: a) preliminary, b) after 9 min, and c) after 12 min. Lateral roentgenograms: d) preliminary, e) after 9 min. Good spontaneous filling of hepatic duct and its branches; common bile duct only faintly visible. Layer formation of contrast medium (arrow) in common bile duct (e) whose contours are blurred (b).

In the first ten trials the cholecystokinin was given intravenously by injection; this technique, however, was abandoned and replaced by intravenous drip, 3 mg of the substance dissolved in 500 ml of normal saline being administered over a period of about 20 minutes. Films were taken ten seconds, one minute, three minutes, and then every three minutes throughout the duration of the drip. After termination of the latter, a further two films were obtained.

Findings

Prior to emptying. Parts of the biliary ducts were faintly outlined even in the first roentgenogram in a good many cases. This 'spontaneous' filling, *i. e.* filling before the instillation of cholecystokinin was more often observed with the patient tilted head downwards than in the horizontal position (Diagram 2). In the former position the hepatic duct filled more frequently than the common bile duct (Fig. 1, a and d), whilst in the latter position the reverse was true. The probable explanation of this observation was that the specific gravity of the bile varied, *i. e.* the densest

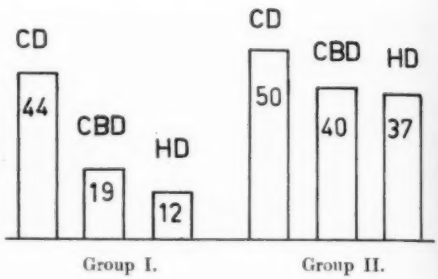

Diagram 3. 'Spontaneous' filling of bile ducts in the presence of gallstones (group II, 70 cases) as compared with absence of gallstones (group I, 32 cases). The figures in the columns denote percentages of cases.

bile filled the most inferior parts of the gallbladder and ducts. With the head tilted downwards the densest bile filled the ampullary part of the gallbladder and was seen to pass more often into the hepatic and common bile ducts than when the patient was in the horizontal position. In the horizontal position the common bile duct was seen to run at a lower level than the hepatic duct, whilst with the head tilted downwards the former was often found to run at the same or a slightly higher level than the latter.

A comparative study of the findings in Groups I and II showed that spontaneous filling occurred more often in Group II than in Group I (Diagram 3). The explanation of this finding might have been that owing to an increase in the tone of its walls the gallbladder which contains calculi tends to empty with greater ease than does the normal organ.

During emptying. The gallbladder generally emptied about half of its contents of contrast medium. Individual variations were observed, however. In some cases the gallbladder emptied completely, following the installation of a quarter of the usual dose of cholecystokinin, whilst in 2 cases it failed to empty despite the fact that the dose was doubled. In one of these latter cases the gallbladder contained a solitary calculus the size of a pea which probably obstructed the outflow of bile. In the other, no calculus was demonstrated. In both cases the films showed that the shape of the flaccid gallbladder altered; from being elongated and irregular it became shorter and rounder, as well as regular and oval in shape. The alteration in the appearance was no doubt due to an increase in the tone of the muscle of the gallbladder wall, which proves that the muscle reacted to the stimulus of cholecystokinin but was not able to bring about emptying. In the case in which no calculus was demonstrated the cystic duct was blocked but the nature of the obstruction was not apparent. BRODÉN (1956) reported several cases in which the gallbladder failed to empty despite the fact that no calculi were demonstrated. BACKLUND (JORPES et coll. 1957) encountered identical conditions in 8 of 59 cases.

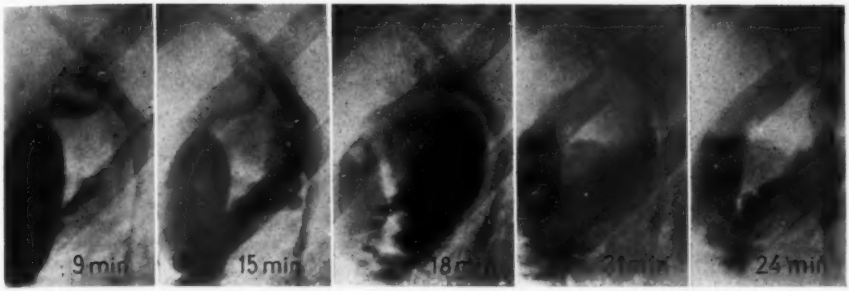

Fig. 2. Solitary gallstone moving towards and blocking the cystic duct. 18-min film shows medial displacement of common bile duct caused by duodenal peristalsis.

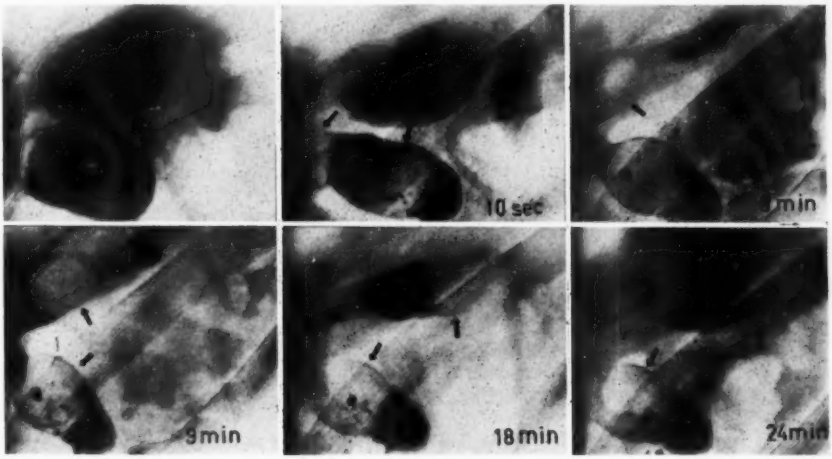

Fig. 3. Two gallstones. Contraction of gallbladder causes one of them to move towards the cystic duct.

There was no appreciable difference between Groups I and II as regards the rate of emptying and the amount of contrast medium expelled.

Of the 70 cases in Group II a calculus partially obstructed the emptying in 32. In most cases one or more calculi were carried with the bile to the point of origin of the cystic duct and there obstructed it (Fig. 2). A large fixed calculus was occasionally seen in the centre of the gallbladder; in these cases only the non-obstructed part of the organ emptied and it became so narrow that it was impossible to identify the line of demarcation between the cystic duct and the gallbladder. In one case it was observed that contraction of the gallbladder resulted in the movement of a large calculus right through the gallbladder to the cystic duct which it

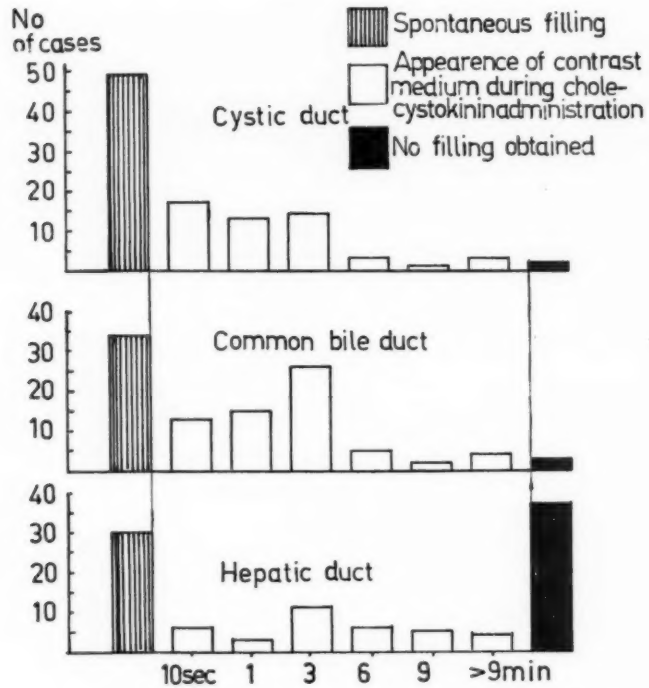

Diagram 4. The case material, 102 cases, divided according to the interval between onset of drip and filling of bile ducts.

blocked (Fig. 3). In no case was a calculus seen to move right through the cystic duct into the bile duct during the emptying.

Discomfort experienced during emptying. Of the 102 patients in this series 45 experienced discomfort of varying degree. Of the 70 patients in Group II, 30 experienced pain or discomfort. Of these latter cases, 11 complained of diffuse symptoms or of 'rumbling', but no pain. In the remaining 19 cases there was either distress in the right hypochondrium, which resembled in character the patient's usual biliary colic, or the symptoms preceding the latter. However, all these symptoms disappeared on termination of the drip. Of the 19 patients who had pain resembling biliary colic, 15 developed it in conjunction with obstruction of the cystic duct by a calculus. The pain was generally felt simultaneously with, or shortly before, the obstruction. It may therefore be assumed that the obstructing calculus accounted for the pain in these cases. On the other hand, in a

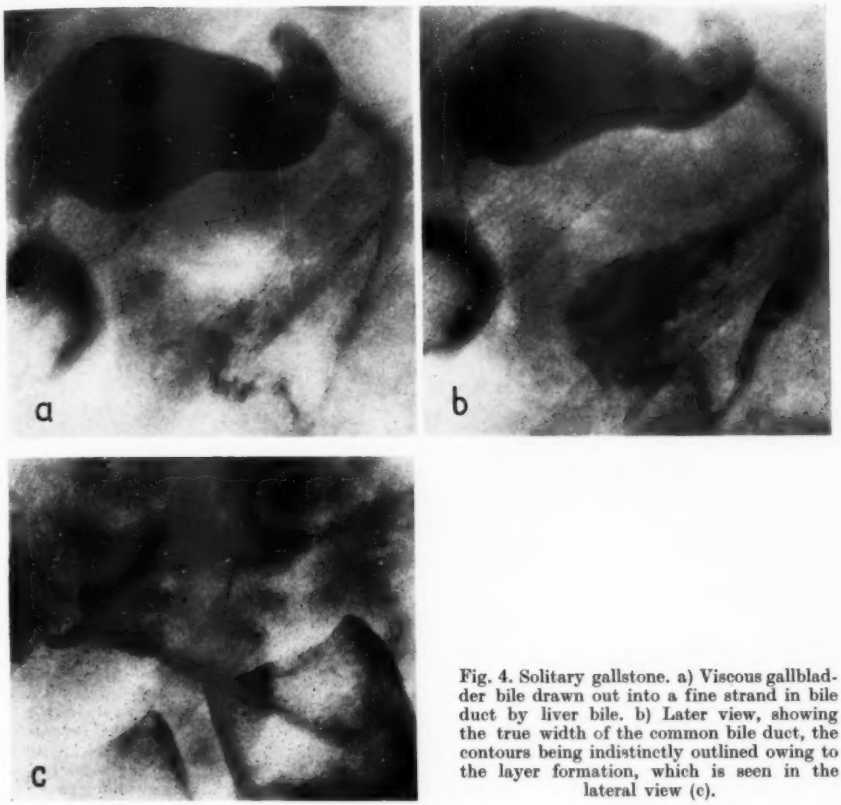

Fig. 4. Solitary gallstone. a) Viscous gallbladder bile drawn out into a fine strand in bile duct by liver bile. b) Later view, showing the true width of the common bile duct, the contours being indistinctly outlined owing to the layer formation, which is seen in the lateral view (c).

further 17 cases of obstruction of the cystic duct neither discomfort nor pain was experienced.

Of the 32 cases in Group I, the patient complained of distress in 15: in 11 of these there was slight diffuse discomfort, and in the remaining 4 the discomfort was more severe and resembled biliary colic.

Filling of the bile ducts during emptying. The 6 or 9-minute films showed optimum filling of the bile ducts. In some cases the ducts began to fill within ten seconds from the start of the drip (Diagram 4). In later trials it was found that the pain caused by the needle may induce contraction of the gallbladder. This may be an explanation of the rapid filling of the bile ducts. It was also shown in these tests that the common bile duct

began to become contrast-filled following the instillation of only 0.03 mg of cholecystokinin *i. e.* 1/100 of the total dose.

Of the 102 cases in the present series the common bile duct failed to fill in 3 cases only. The hepatic duct failed to fill in 25 cases, or 42 per cent, examined in the horizontal position, and in 11 cases, or 26 per cent, examined with the head tilted downwards. It is therefore suggested that the hepatic duct fills more frequently in the latter position and that demonstration of this duct is no evidence of biliary disease. Visibility of the bile ducts varied. Of the 99 cases in which the common bile duct filled, it was so clearly outlined in 17 cases that even small calculi, if present, should have been visible; in 35 cases the degree of contrast-filling should have enabled identification of 'calculi of clinical significance', *i. e.* calculi larger than 2 to 3 mm in diameter. In 47 cases the width and shape of the common bile duct could be assessed but it was not sufficiently clearly outlined to enable identification of calculi.

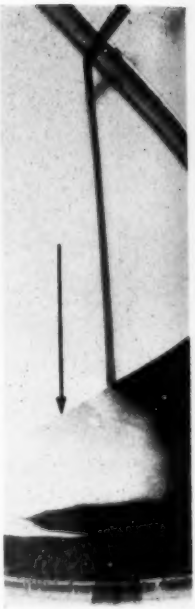

Fig. 5. Model used to study gallbladder bile flow. Through nozzle at top viscous bile is slowly extruded into a current of water (arrow). No mixing of streams; the bile is drawn out into a fine strand.

There was no appreciable difference between Groups I and II in respect to the degree of contrast-filling of the biliary ducts.

The ducts were less clearly outlined in the 5 cases in which the patient was examined in the prone position. In this posture the densest bile was found to accumulate in the fundus, whilst the less dense bile was seen to fill the ampulla. The latter was then expelled first into the ducts, whilst the former did not participate in their filling unless the gallbladder completely emptied its contents of contrast medium. In the supine position, however, the densest bile was expelled first.

Width of the bile ducts during emptying. The widths of the hepatic and common bile ducts were measured directly from the films. Owing to individual variations determination of the true width involved difficulties; various factors account for these variations. One factor is the previously mentioned difference in the specific gravity of the bile, one layer floating, so to speak, on top of the other. This layer formation was often quite marked in the ducts because in the dorsal position the 'contrast' bile of highest specific gravity was the first to flow into the ducts which contain liver bile of relatively low specific gravity. The gallbladder bile was often

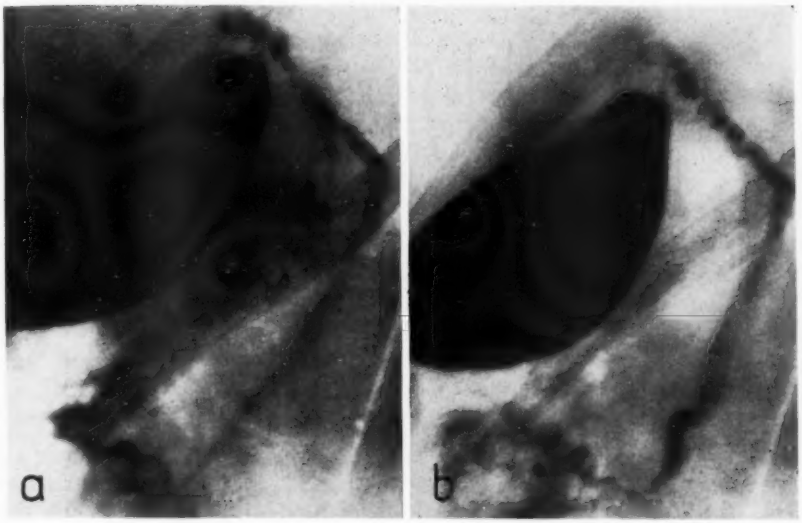

Fig. 6. Normal gallbladder. a) Patient in expiration. b) Shallow inspiration producing alteration in length and width of common bile duct.

seen to sink to the bottom of the duct where it formed a layer which flowed either in the direction of the ampulla of the bile duct, or in the hepatic duct towards the liver, depending on the inclination of the ducts in the individual cases (Fig. 4 b and c). In films taken in the vertical projection the ducts were indistinctly outlined; as filling of the ducts increased during emptying of the gallbladder, and the gallbladder bile began to mix with the liver bile, the ducts became more clearly outlined (Fig. 1, b and c). It is only at this stage that the true width is shown.

Another source of error associated with determination of the width of the ducts is the variation in length and appearance of the cystic duct. The latter was often found to unite at a very low level with the hepatic duct, running parallel with it over quite a distance; it is then easily confused with the common bile duct. Moreover, the cystic duct may be superimposed upon part of the hepatic and common bile ducts resulting in the latter appearing to be wider than normal. The common bile duct occasionally appeared to be sharply outlined and very narrow (Fig. 4 a); this phenomenon was usually of very short duration. Experiments on models showed that viscous gallbladder bile injected slowly into a passing stream of water did not mix with the water, but, being gummy, was drawn out into a fine strand; this is probably what happens in the common bile duct when the opaque bile from the contracting gallbladder flows into the passing liver bile (Fig. 5).

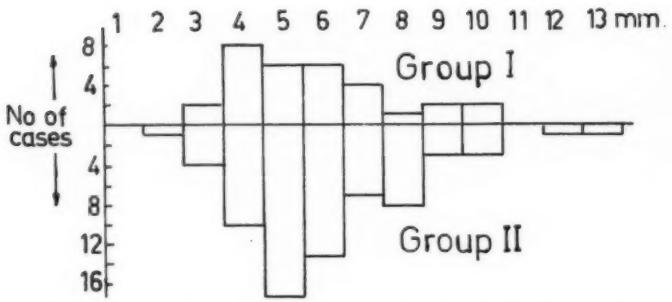

Diagram 5. Diameter of the hepatic and common bile ducts (considered together). In group I (31 cases) the average width was 5.7 mm, in group II, 6.0 mm.

Further sources of error are variations in the true width and length of the ducts during emptying; even moderate respiratory movements may cause alterations in width and length (Fig. 6). Duodenal peristalsis also affects the ducts, and distension of the duodenum may displace them medially (cf. Fig. 2, 18-minute film).

Peristalsis of the hepatic and common bile ducts was not demonstrated in this investigation. However, contraction at the junction of the cystic duct with the hepatic duct, simultaneously with contraction of the gallbladder and cystic duct was observed. With the exception of the pars intestinalis, muscle fibres are sparse in the hepatic and common bile ducts, but the muscle fibres in the cystic duct run into these ducts, where they divide into branches; these branches may account for the contractions at the junction of the two ducts.

There are obviously many sources of error associated with the assessment of the width of the hepatic and common bile ducts. Some of these may be avoided by taking a sufficiently large number of films at regular intervals during emptying of the gallbladder.

The width of the ducts was measured just below the medial part of the 'S' which is formed in the majority of cases, *i. e.* just below the point of junction; where the two ducts united at an abnormally low level the corresponding part of the hepatic duct was measured. There was no appreciable difference between Groups I and II in respect to the width of the ducts, the average width being 6 mm in both groups (Diagram 5).

Conclusions

The total amount of contrast medium in the ducts and its distribution in them depend on the patient's position during the contraction of the gallbladder. Filling of the hepatic duct is no evidence of biliary disease.

The contrast-filling of the hepatic duct depends mainly on the position of the duct in relation to the horizontal plane.

The degree of contrast-filling of the ducts depends on the power of concentration of the gallbladder. If the latter is satisfactory the biliary system is more clearly outlined than in intravenous cholangiography. The presence of calculi does not interfere with the ability of the gallbladder to empty.

Emptying of the gallbladder under the stimulus of cholecystokinin occasionally gave rise to symptoms which resembled those which the patients usually experience. This suggested the presence of biliary disease.

SUMMARY

Emptying of the contrast-filled gallbladder following the administration of cholecystokinin was studied in a series of 102 cases with symptoms which might have been referable to biliary disease. The relationship between the patient's position during the examination and the degree of contrast-filling of the ducts was investigated. Factors which may give rise to misinterpretation of the appearances are discussed.

ZUSAMMENFASSUNG

Die Entleerung der mit Kontrast gefüllten Gallenblase nach Administrierung von Cholezystochinin wurde in 102 Fällen studiert, welche sämtliche Symptome aufwiesen, die auf einer Erkrankung der Gallenwege beruhen könnten. Die Beziehungen zwischen der Lagerung des Patienten während der Untersuchung und des Grades der Kontrastfüllung der Gallengänge ist untersucht worden. Faktoren, die zu einer Fehldeutung des Aussehens Veranlassung geben könnten, werden diskutiert.

RÉSUMÉ

Sur une série de 102 malades présentant des signes fonctionnels pouvant être dûs à une affection biliaire, l'auteur a étudié l'évacuation de la vésicule biliaire remplie de contraste après administration de cholécystokinine. Il a étudié les relations entre la position du malade au cours de l'examen et le degré de réplétion des voies biliaires par le contraste. Il examine les facteurs qui peuvent donner lieu à une erreur d'interprétation des images.

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VENOGRAPHIC AND SCINTILLOGRAPHIC DEMONSTRATION OF LIVER METASTASES

by

C. G. Helander, L. Jonsson, L.-G. Larsson, Å. Lindbom and *P. Ödman*

A method for the roentgen examination of the hepatic veins after the injection of a contrast medium was described in 1951 by RAPPAPORT who, with the help of a guide, introduced a catheter into the hepatic veins of dogs. TORI (1953) demonstrated that it was possible to inject contrast medium into the hepatic veins from a catheter introduced through an elbow vein. Using this method, several authors have studied hepatic veins in human subjects angiographically (SERVELLO and DALLA PALMA, CELIS et coll., NEY, and others). The method has not previously been used for the diagnosis of liver metastases.

Many intravenously injected compounds are concentrated in the liver due to metabolism in the liver cells or to uptake in the reticuloendothelial system. If the substance is labelled with a gamma-emitting isotope, its distribution within the liver may be studied in vivo (STIRRETT et coll., 1953, FRIEDELL et coll. 1957). The most convenient measuring instrument is an automatic scanning scintillation counter; due to the inability of tumour tissue to concentrate the radioactive substance, alterations may be found in the liver scintillogram when metastases are present (FRIEDELL et coll. 1957).

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a

b

Fig. 1. a) Retrograde contrast-filling of right main hepatic vein. A hooked non-opaque catheter has been introduced into right femoral vein and advanced through inferior vena cava into the orifice of the hepatic vein. Normal case. No deformities.

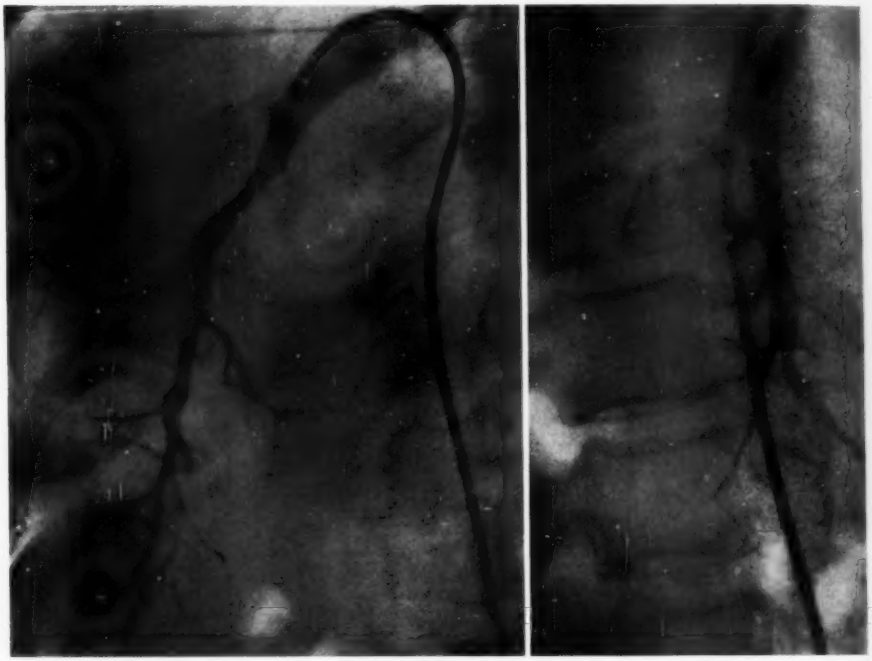
b) Another normal case. A more medial branch is filled. No deformities.

The aim of the present investigation was to study the normal and pathologic venographic and scintillographic appearances of the liver. Two groups of patients were therefore chosen: 1) without suspected liver metastases, and 2) with clinically verified or probable liver metastases.

Venographic technique. For catheterization of the hepatic veins we employed a method somewhat different from those previously reported. The catheter was of the type described by ÖDMAN, consisting of polythene and a radiopaque material. The end of this catheter, which had an overall length of 60 to 65 cm, was heated and bent into an arc of a circle with a radius of about 2 cm; the terminal part, about 1 cm long, was kept straight. The catheter was inserted by SELDINGER's method percutaneously into the right femoral vein in the groin. By means of a metal guide inside the catheter, the curved end was then straightened and the catheter advanced

Fig. 2. Retrograde hepatic venography. Forced injection into a small branch. Contrast medium passes back through hepatic capillaries, filling some fairly large branches of the portal vein.

through the inferior vena cava to the right atrium. On withdrawal of the metal guide, the end of the catheter reverted to its former curved shape with the crook located in the atrium. It could be rotated while in that position, so that the tip pointed in different directions. On retraction of the catheter under fluoroscopic control with the crook pointing forwards, it usually entered one of the hepatic veins quite easily. Reinsertion of the metal guide then enabled us to advance the catheter once more into the atrium and, on retraction with the tip pointing in a different direction, to introduce it into another hepatic vein. These manipulations usually caused no discomfort, though a few patients reported slight pain on passage of the catheter through the vena caval hiatus. In one-half of the series we succeeded in introducing a catheter into three different hepatic veins, in one-fifth, into only one vein. In 2 cases out of 25 we failed to pass the catheter into any hepatic vein.



a b

Fig. 3. Retrograde hepatic venography with an opaque catheter introduced percutaneously into right femoral vein. Marked deformities of vessel caused by multiple metastases in liver. Examination by means of automatic film changer with a. p. (a) and lateral (b) projections at the same contrast injection. The two venograms exposed with an interval of about 0.3 sec.

In the examination of certain heavily built and obese patients an image amplifier was very useful since with conventional fluoroscopy we were able to pick up the catheter on the screen only with difficulty. In many cases in which the position of the catheter was hard to judge, rapid injection of about 5 ml contrast medium during fluoroscopy helped us to localize the catheter tip, either in the vena cava or in a large or small hepatic vein. For the venographic examination itself, 15 to 30 ml Urografin 30 or 45% were injected manually at the rate of about 5 to 8 ml per second. The amount was adjusted to the size of the vessel in which the tip was situated. At least three exposures were made in rapid sequence, either with a simple cassette changer or with an automatic film changer. In a few cases films were obtained during a single injection of contrast medium with a film changer in two planes at right angles to each other

a

b

Fig. 4. a) Retrograde contrast-filling of right main hepatic vein. The contrast medium penetrated into some branches of portal vein and also 'charged' liver parenchyma. Filling defect (arrow) at the lateral border of the liver, probably caused by a metastasis. b) Retrograde hepatic venography. Deformities of main branches of left hepatic vein and filling defects in the liver parenchyma caused by fairly small metastases.

and with alternate exposures in anteroposterior and lateral projections. It was then found that the maximum contrast-filling of the hepatic veins usually had a duration of 1 to 2 seconds. The emptying time varied between 2 and 5 seconds. This applied to the injection of 30 ml contrast medium at the rate of 8 ml per second into one of the large branches of the hepatic veins. At first we gave the injections during Valsalva's manoeuvre, but after comparative examinations with and without the latter procedure had shown no difference in contrast-filling of the hepatic veins, we instructed the patients simply to hold their breath and not to strain. In no case did we find any complications attributable to the venographic procedure.

Scintillographic technique. An automatic scanning scintillation counter as previously described was used (JONSSON, LARSSON & RAGNHULT 1957, LARSSON and JONSSON 1957). A tracer dose of 0.5 to 1.0 mC colloidal Au^{198} was injected intravenously. Due to reticuloendothelial activity

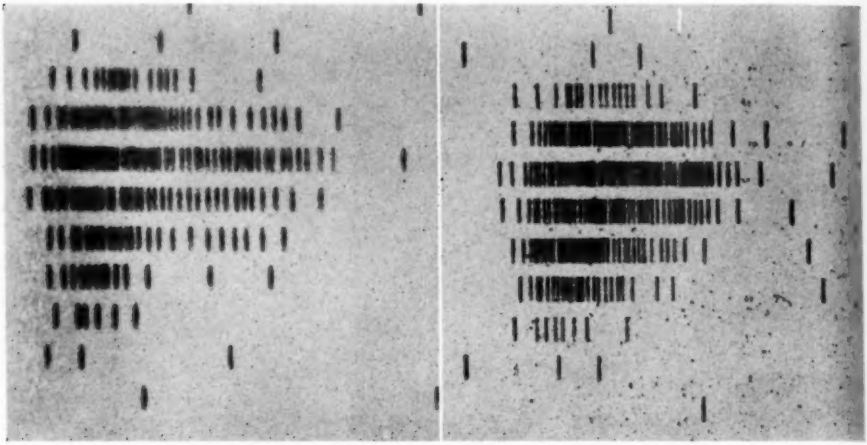


Fig. 5. Hepatic scintillograms in two cases without liver metastases.

about 90 per cent of intravenously injected colloidal gold is rapidly taken up by the liver, the remainder being absorbed by the reticuloendothelium in the spleen and bone marrow (SHEPPARD et coll. 1947, HAHN et coll. 1957). A scintillogram was obtained over the liver region, using a collimator with a diameter of 1.2 cm and a length of 8.5 cm. The distance between two adjacent parallel lines was 2.5 cm and the speed of the detector about 40 cm per minute. The scintillogram was recorded on paper to a scale of 1:5 with a mechanical printer. Two scintillograms with different scaling factors (fraction of registered impulses) were usually made. The scintillation counter was provided with a single channel pulse height analyzer and the channel was adjusted to the 411 keV photon peak of Au^{198}.

Material

Both hepatic venography and scintillography were undertaken in a fairly large number of patients without liver metastases (the venographic series contained 15 cases of this type). In order to study pathologic appearances, concurrent venographic and scintillographic examinations were undertaken in six cases with malignant tumours and clinical signs of liver metastases (palpable nodular liver and/or jaundice). A further two cases with malignant tumours were investigated; they showed no clinical evidence of liver metastases, although these were strongly suggested due to the generalized nature of the neoplastic disease.

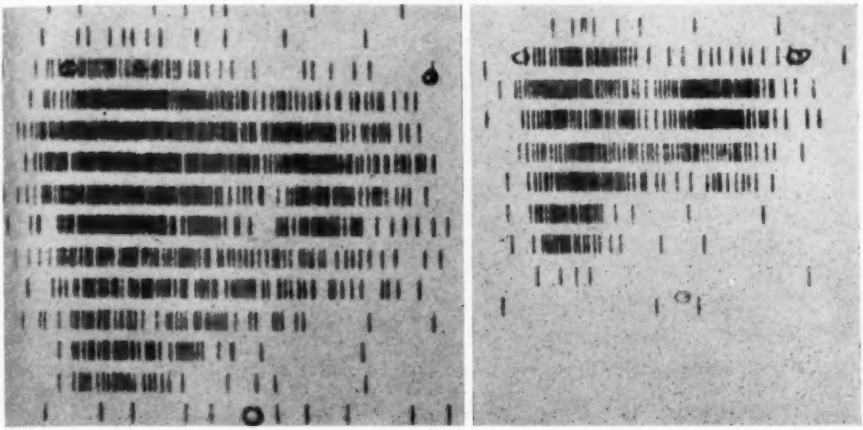


Fig. 6. Hepatic scintillograms in two cases with liver metastases: enlargement of the liver and tumor defects.

Venographic findings

When the catheter was inserted with its tip at least a few centimeters inside the origin of a hepatic vein, the injection of contrast medium usually produced filling of all relevant branches (Fig. 1). When it had a more peripheral location or had entered a small branch of a hepatic vein, contrast-filling was obtained of the very finest branches and the capillaries, and via the latter the contrast medium passed in some cases to branches of the portal vein. Contrast-filling of portal branches with calibers of up to about 5 mm was obtained in some cases in this way (Fig. 2).

In 5 of the 6 patients with clinically demonstrable liver metastases, the hepatic venograms disclosed definite changes. Rounded indentations bulging into the lumen of the large branches of the hepatic veins were observed and smaller branches often showed curved displacement (Figs. 3 and 4 b). In 3 cases there were both deformation of the branches of the vein and contrast defects in the liver parenchyma (Fig. 4). In the sixth case only the right hepatic vein became filled, and no pathologic changes were detectable; the scintillogram disclosed a process in the left lobe. In one of the two cases with suspected though not clinically verified liver metastases, the venograms revealed relatively small multiple metastases; in the other, the examination yielded negative results.

Scintillographic findings

The scintillograms in the control cases revealed evenly scattered spots over the liver region (Fig. 5). In each of the six cases with clinically verified liver metastases the liver scintillogram was abnormal. In some cases

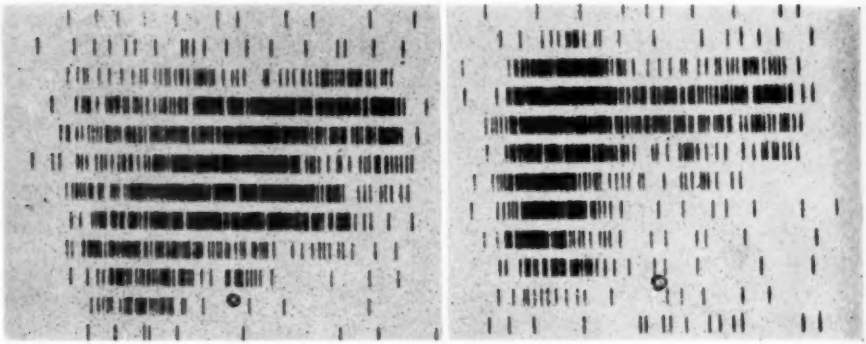


Fig. 7. Hepatic scintillograms in two other cases with liver metastases: enlargement and irregular contour of the liver.

defects or areas with a reduced density of spots were observed in the scintillograms (Fig. 6), and in some cases the contour of the liver was very irregular (Fig. 7). In the two cases without clinically demonstrable liver metastases the liver scintillogram was negative; in one of them the venogram, as mentioned above, revealed multiple metastases.

Discussion

Both hepatic venography and scintillography may be used for the demonstration of liver metastases. The two methods have various advantages. With the venographic method in some cases only a limited part of the liver can be examined; hence even large metastases situated outside that segment may be overlooked. On the other hand, fairly small multiple metastases, if situated close to the contrast-filled veins, may be diagnosed.

With the scintillographic method the whole liver is examined and the chance of missing large metastases is probably small. Yet the metastases must reach a considerable size if they are to be demonstrated scintillographically; otherwise they will be concealed by the overlapping normal liver tissue.

Of the two examinations the scintillographic one is by far the simpler and probably the more suitable for routine use. It could be greatly improved technically by the use of a more suitable collimator system, detector speed, line distance, and scale for registration, than those employed in this preliminary investigation. Methods for bettering the contrast in the scintillogram (MacIntyre et coll. 1957, Kuhl et coll. 1956) might also increase the diagnostic value of the method. In doubtful cases the more elaborate venographic method might be of definite value, and the two

methods in conjunction would certainly yield most information. In order to determine the diagnostic value of the methods it will also be necessary to study cases of malignant tumors without clinical signs of hepatic metastases *i. e.* those in which the diagnosis of liver metastases really is of practical importance.

SUMMARY

Methods of performing hepatic venography and liver scintillography are described. The normal appearances and those encountered in cases of liver metastases are discussed with special reference to a total material of 25 cases. The scintillographic method is probably the more suitable for routine employment; venography may, however, yield information in doubtful cases.

ZUSAMMENFASSUNG

Methoden zur Ausführung von Lebervenographien und Leberscintillographien werden beschrieben. Das normale Aussehen derselben und die Befunde in Fällen mit Lebermetastasen werden unter besonderer Bezugnahme auf ein Gesamtmaterial von 25 Fällen besprochen. Die scintillographische Methode ist wahrscheinlich für den täglichen Gebrauch besser geeignet; die Venographie kann jedoch in zweifelhaften Fällen Informationen geben.

RÉSUMÉ

Les auteurs décrivent les méthodes de phlébographie hépatique et de scintillographie du foie. Ils étudient les aspects normaux et ceux qu'ils ont trouvés dans des cas de métastases hépatiques, d'après un total de 25 cas. La méthode scintillographique est probablement celle qui convient le mieux en pratique courante; la phlébographie peut cependant fournir des renseignements dans les cas douteux.

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ORGANIC MATRIX OF URINARY CALCULI

Microradiographic comparison of crystalline structure with microscopic and histochemical studies

by

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Microradiography, or radiomicrography, has extended roentgenography into the realm of the microscopic. Studies have been made of the kidney, the gastrointestinal tract, the spleen, the lung and the brain after injection of contrast media into the vascular structures (1, 10, 9, 2). Many studies have also been made of inorganic materials, including pleural calcification and bone (6). BOHATYRCHUK (3) has noted that microradiography gave a more reliable depiction of microscopic detail of bone than did similar sections prepared by conventional decalcification and histologic techniques.

Previous studies of more than 1,200 decrystallized urinary calculi have demonstrated the presence of a mucoprotein matrix in all specimens (4). The histochemical (5) and biochemical (7) features of the matrix have been defined. Microradiographic studies of urinary calculi have also been reported (8). The present study was designed to compare microradiograms

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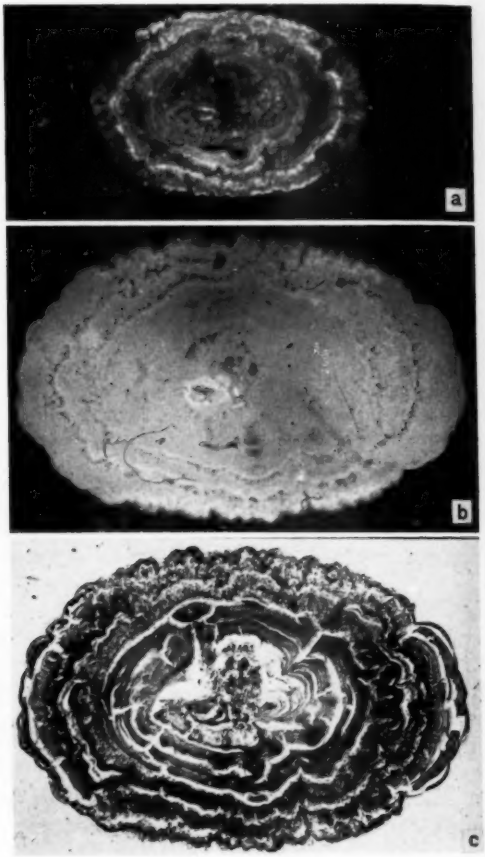


Fig. 1

Calcium oxalate calculus from ureter. Original size 9 × 15 mm.

a) Photograph of center section from gross specimen.

b) Microradiogram of (a).

c) Unstained matrix remaining after complete decrystallization of (a).

of untreated calculi with microscopic and histochemical studies of the identical sections after decrystallization. Such a study should further elucidate the crystal-matrix interrelations in calculi.

Method of study

Forty-six different urinary calculi of various crystalline composition were serially sectioned. Representative sections were embedded in Carolina embedding plastic, a clear polyester type resin, and mounted on the surface of a rigid sheet of the plastic. These sections were polished on a microtome stone to a thickness of approximately 40 to 100 mμ.

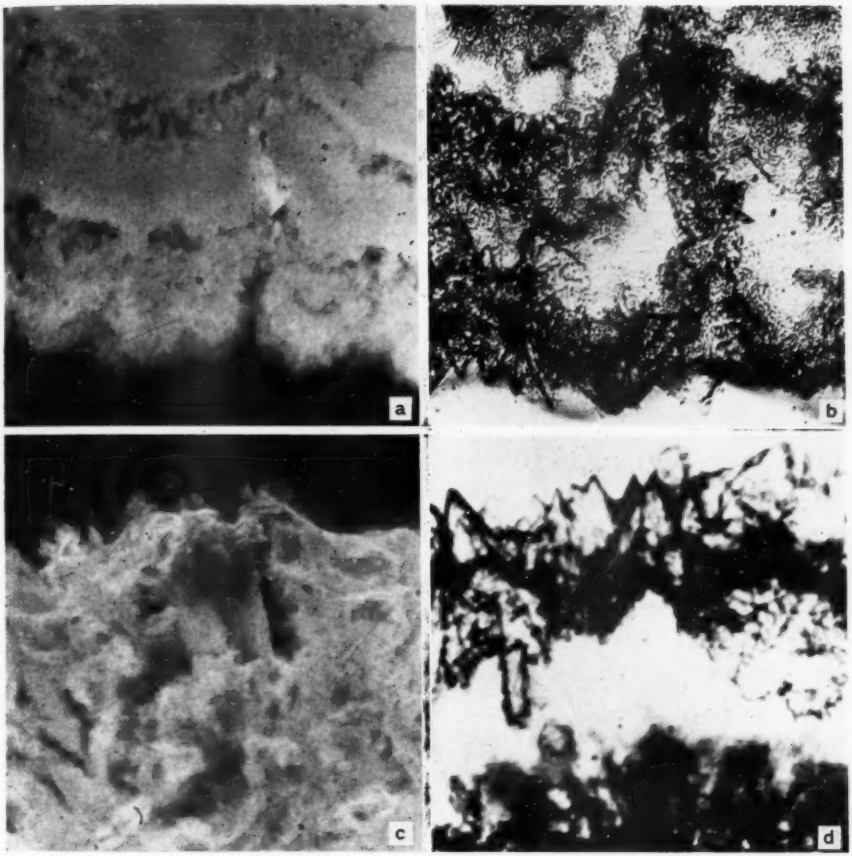


Fig. 2

a) Microradiogram of same specimen as in fig. 1a, marginal section. Crystals are largely calcium oxalate monohydrate. There is a single radial striation of more roentgen opaque basic calcium phosphate (apatite).

b) Unstained matrix remaining after decrystallization of (a). Radial striation of matrix corresponding with area of apatite deposition.

c) Microradiogram of margin of specimen in fig. 1a, showing calcium oxalate dihydrate.

d) Photograph of unstained matrix remaining after decrystallization of (c). Film of matrix covers large oxalate crystals, and remains after crystals are dissolved.

The thin sections of calculus were thus exposed on the surface of a rigid plastic backing, approximately 3 mm in thickness. The bare section of stone could be brought into direct contact with photographic plates, examined with the petrographic microscope, or exposed to various decrystallizing solutions or histochemical reactions.

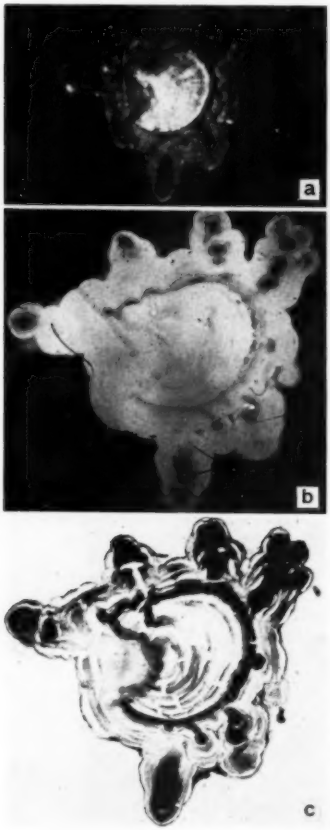


Fig. 3. Calcium oxalate monohydrate 'jack-stone' from bladder. Original size 10 × 12 mm.

a) Photograph of center section from original specimen.

b) Microradiogram of (a). Less dense crystallization in central core of each frond.

c) Unstained matrix remaining after decrystallization of (a). Dense matrix fills spaces in central core of each frond.

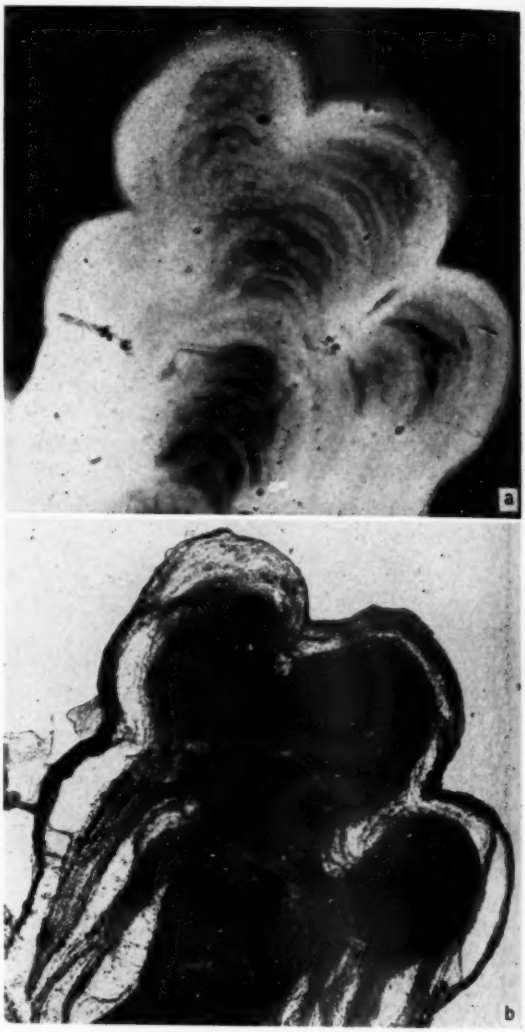


Fig. 4

a) Microradiogram of trident frond from specimen in fig. 3 b.

b) Unstained matrix remaining after complete decrystallization of (a).

High resolution spectrophotometric plates and X-ray diffraction apparatus were used to obtain microradiograms of sections from the various urinary calculi. Physical factors employed in microradiography were: either molybdenum target: 35 kV, 20 mA, 40 min open port, 76 cm target-to-film distance, or chromium target: 40 kV, 20 mA, and 8 min exposure time. The resolution of these plates is approximately 1,000 lines per millimeter, so that a satisfactory magnification of 500 to 1,000 times is possible with minimal graininess.

These same sections of urinary calculi were then decrystallized by immersion in various decrystallizing solutions, as previously described (7). The filamentous nature of the matrix in cystine calculi required a coating of semipermeable collodion over the exposed surface of the section prior to decrystallization, to prevent loss of the matrix material. Similar coatings of collodion were found to be unnecessary for other types of calculi since the matrices remained intact. Decrystallization was adjudged complete when the specimens became translucent and when crystals were no longer visible on microscopic examination. Crystal types were identified with the aid of the petrographic (polarizing) microscope. Histochemical studies utilizing the Schiff's periodic acid leucofuchsin, von Kossa, and toluidine blue reactions were then carried out by the previously described methods (5).

The thickness of these sections prepared prior to decrystallization was greater than that normally employed for microscopic study. In order to observe the fine detail of structure and histochemical reactions, adjacent sections from the same calculi were decrystallized without embedding in plastic. These sections were then embedded in paraffin and sections 8 to 10 microns in thickness were studied by the above histochemical techniques.

The crystalline composition of the various areas of each section was determined by a combination of several techniques since no one method is satisfactory for the *in situ* detection of all types of crystals. The relative roentgen density of the various crystal structures has been exhaustively studied by LAGERGREN utilizing X-ray diffraction techniques (8). Survey of the microradiograms thus gave a valuable guide to areas of varying crystal composition and an indication of the type of crystal present. With the exception of basic calcium phosphate (apatite) the petrographic microscope gave reliable identification of the various crystals *in situ*. Apatite is readily identifiable by polarized light when it is present in layers between the fibrous matrix, but where there is a dense organic membrane much apatite can be present without detection of the characteristic blue spectrum. In such areas the combination of maximal roentgen density, strongly positive von Kossa reaction, crystals of submicroscopic size, and failure to give a specific diffraction pattern with the polarizing microscope served to identify the presence of apatite. Chemical analysis of material from adjacent sections of the calculi and microscopic appearance of the crystal configuration were additional evidence of the composition.

Results

Calcium oxalate (*Figs. 1 to 4*). The intimate structure of these calculi was varied, but in general consisted of concentric rings of irregularly dense crystalline material. The surface often had a serrated margin or lace-like

scalloping of large calcium oxalate dihydrate crystals. The calcium oxalate monohydrate calculi appeared to be more compactly crystalline, often with regular concentric rings in close apposition.

The decrystallized specimens revealed no microscopically recognizable crystals of calcium oxalate, but the von Kossa stains nevertheless indicated small deposits of von Kossa-positive material along the margins of many of the fibrils. The concentric laminations of the organic matrix were uniformly present from the center to the surface of the calculus and they clearly coincided with the crystalline arrangements in the microradiograms (Figs. 1 and 2). Radial striations of monohydrate crystals were clearly and consistently related to radial laminations of matrix. Little metachromasia with toluidine blue was seen in these specimens, except in those areas where the petrographic microscope or the von Kossa method indicated the possible presence of basic calcium phosphate ('apatite').

The preceding observations suggested a regular arrangement of matrix material, with some distortion due to the growth of large calcium oxalate dihydrate crystals.

Calcium phosphate (hydroxylapatite) (Fig. 5). Calculi in this group exhibited evenly spaced concentric laminations, with very little of the irregularity noted in the calcium oxalate stones. Crystals appeared to be arranged in

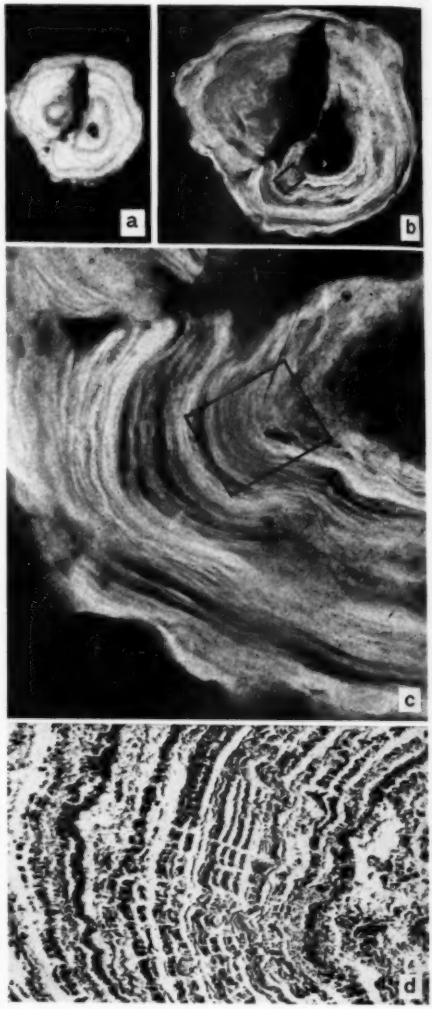


Fig. 5. Basic calcium phosphate (apatite) calculus from ureter. Original size 7 × 8 mm.

a) Photograph of center section of original specimen.
b) Microradiogram of (a). Rectangle is area depicted in (c).
c) Microradiogram of (a). Rectangle encloses area of matrix shown in (d).
d) Photomicrogram of matrix remaining in rectangle of (c) after decrystallization. Toluidine blue-O stain. Fibrils are metachromatic. Von Kossa positive granules remain along the surface and embedded within the fibers of matrix.

these concentric layers with very little radiolucent material between the concentric rings. In general, it was noted that the concentric laminations tended to be ovoid rather than a perfectly circular shape; the smallest ring tended to be quite eccentric.

The decrystallized specimens clearly demonstrated concentric laminations of dense matrix material which were coincident with the areas of greatest roentgen density. The crystalline deposits were therefore on fibrils of matrix, with amorphous matrix material forming the radiolucent area between. The tiny deposits of von Kossa-positive material were aligned with the membranes and fibrils rather than the inter-fibrillar amorphous material. Metachromasia with toluidine blue was common in the fibrils of these calculi but was not demonstrated in the amorphous material. All segments of the matrix gave a strongly positive PAS reaction.

Uric acid (*Figs. 6 and 7*). The pure uric acid calculi were only faintly opaque by this method of microradiography and no details of crystalline structure could be detected other than the laminations and radial striations visible by conventional optics (Fig. 6 a). The central areas of some of these calculi apparently contained a more dense aggregation of crystals than the peripheral body of the stones since they were of greater roentgen opacity.

The decrystallized specimens contained a uniform distribution of matrix in regular concentric laminations from center to surface. These layers or 'membranes' were closely spaced with little interfibrillar amorphous material. Radial striations of crystals were clearly related to radial laminations of matrix. The entire matrix was PAS positive and uniformly orthochromatic (blue) with toluidine blue. The decrystallized matrix formed approximately 2 per cent of the weight of the calculi and contained as much as 35 per cent inorganic ash of which 22 per cent was calcium and 2 per cent was phosphorus. The von Kossa stains gave no positive granules in this type of matrix.

Mixed calculi (*uric acid, calcium oxalate, and calcium phosphate* (*Figs. 8 to 10*). Roentgenographically these calculi illustrated the heterogeneity of the various calcium containing crystalline deposits, with the exception of large areas of radiolucent uric acid deposits. The specimen selected for illustration was a large branched calculus, which filled the renal pelvis. The central portion of this calculus was a composite of many centers of crystallization, each having numerous concentric rings and the whole grouped together by surrounding layers of radiolucent matrix material. These central 'nuclei' were composed largely of calcium oxalate monohydrate with some calcium phosphate. The radiolucent areas were uncrystallized matrix or matrix containing uric acid and urates. Near the surface were thin layers of calcium phosphate, which gave a scalloped appearance.

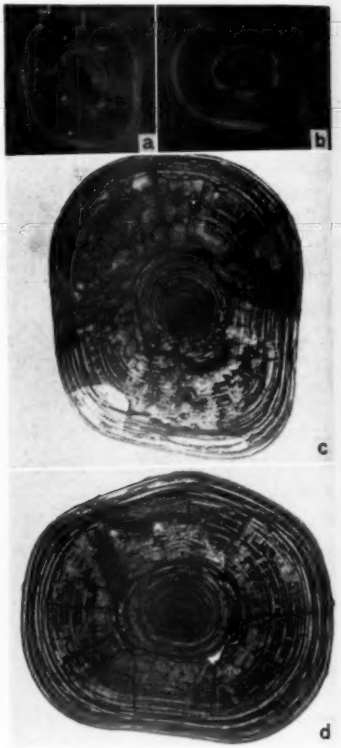


Fig. 6

Two uric acid calculi from bladder of same patient, original size 8 × 10 mm, representative samples of a group of 16 calculi removed from the bladder at one time. The similarity of structure suggests that they may have formed, or increased in size, simultaneously.

a) and b) Photographs of center sections of original specimens. Narrow concentric laminations which appear white are basic calcium phosphate crystals. Dark center areas are dense deposits of uric acid.

c) and d) Matrices of completely decrystallized specimens treated with Periodate Schiff Leucofuchsin reaction (PAS). Radial striations of matrices correspond to radial striations of original calculi in (a) and (b). Apatite crystallization coincides with the most dense laminations of matrix.

Following decrystallization, the distribution of the matrix fibrils and membranes reflected the crystalline arrangement of the calculus. The multinucleated central portion of the calculus consisted of a grouping of small units of matrix composed of concentric layers. Each unit was slightly metachromatic with toluidine blue, PAS-positive, and contained small quantities of von Kossa-positive material. The radiolucent areas of uric acid crystalline deposition were composed of regular layers of dense matrix material arranged in orderly fashion, with little amorphous interfibrillar material. These areas were uniformly orthochromatic (blue) with toluidine blue and the regularity of matrix structure was typical of that observed in pure uric acid stones. Von Kossa stain showed no positive material in the uric acid matrix. The thin zones of apatite calcification near the outer margin of the stone were dense laminations of matrix which were metachromatic with toluidine blue and contained microscopic particles of von

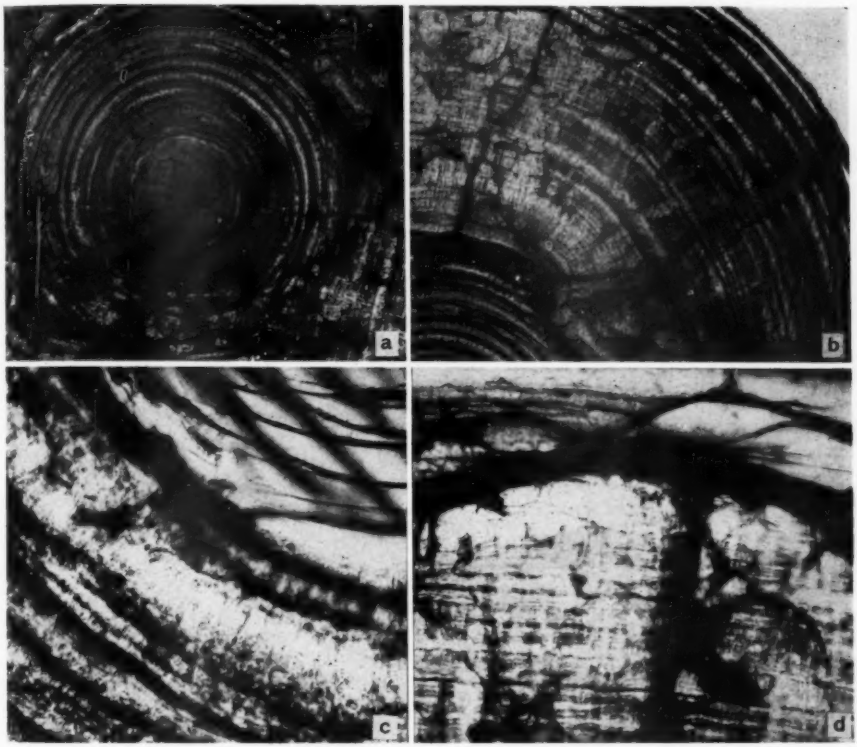


Fig. 7

a) and b) Sectional areas of specimen in fig. 6 c—d. Radial striations and dense laminations which support apatite crystals.
c) and d) Photomicrograms of sectional areas of (a) and (b).

Kossa-positive material. They were otherwise indistinguishable from uric acid matrix, which was also PAS-positive.

Calcium phosphate — magnesium ammonium phosphate calculus (*Figs. 11 and 12*). The concentric dense laminations of these calculi were separated from one another by irregular intervals, alternating with layers that were much less dense and had an amorphous appearance. In some areas, the laminations were close together, giving a region of great radiopacity. As these laminations were followed across the section they were often separated by gradually widening areas of relative radiolucency. The density of a given lamination or membrane appeared to be about equal in any sec-

Fig. 8

Mixed renal calculus of uric acid, calcium oxalate and calcium phosphate.
Original size 40 × 45 mm.

a) Photograph of center section from original specimen.

b) Microradiogram of (a). Spherules in center of calculus are largely calcium oxalate monohydrate with some apatite. Roentgenlucent areas are uric acid although a few such areas are dense masses of amorphous matrix in which few crystals appear. Peripheral laminations of maximal density are basic calcium phosphate (apatite) with some calcium oxalate monohydrate.

c) Unstained matrix remaining after complete decrystallization of (a). Fine fibrils of matrix in areas of uric acid deposition are not fully depicted due to range of contrast in the specimen. Dense laminations of matrix which correspond to areas of apatite deposition. These are clearly metachromatic with toluidine blue-O, whereas uric acid matrix is uniformly orthochromatic (blue).

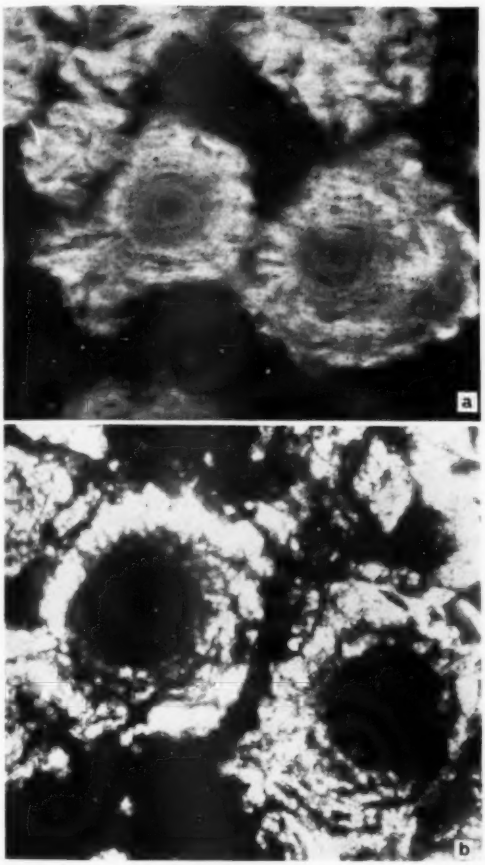


Fig. 9

Same specimen as in fig. 8.

a) Microradiogram of center of fig. 8 a. Laminations of individual spherules of calcium oxalate monohydrate and minimal crystals in the areas between spherules.

b) Photograph of unstained matrix remaining after decrystallization (a). Thickness of specimen (50 mμ) precludes full resolution of detail but laminations of matrix in spherules is clearly evident. Masses of amorphous matrix fill interspaces between spherules, and contain practically no crystals of any type.

tion of the stone, but the over-all radiopacity was directly proportional to whether these apatite covered laminations were closely adjacent or widely separated.

Following decrystallization, it was again clearly demonstrated that in the areas of greatest radiopacity were fibrils or membranes of dense matrix material, in which von Kossa-positive (hydroxylapatite) material was of greatest concentration. The interfibrillar areas contained an amorphous matrix material in which the magnesium ammonium phosphate was deposited. Metachromasia with toluidine blue was most prominent along the fibrils, but the entire matrix material was PAS-positive.

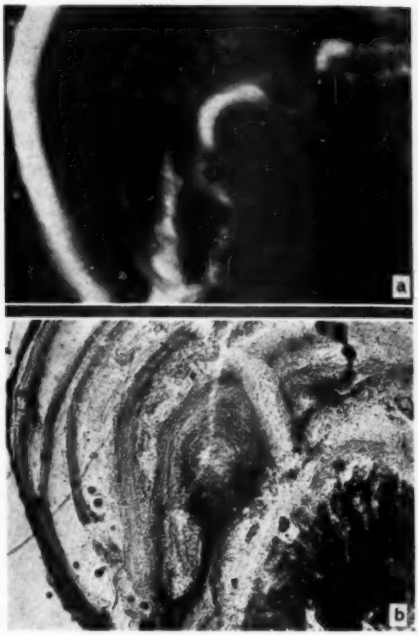


Fig. 10

a) Microradiogram of margin of superior calyceal portion of specimen in fig. 8 a. Areas of uric acid. Laminations of maximal density are basic calcium phosphate. Motley areas of intermediate density are calcium oxalate monohydrate mixed with uric acid crystals.

b) Matrix remaining after complete decrystallization of (a), unstained. Dense laminations of matrix which correspond to areas of apatite deposition and which are intensely metachromatic with toluidine blue-O. Matrix of uric acid crystallization is finely laminated. Areas of dense amorphous matrix have minimal crystal deposition.

Cystine (*Fig. 13*). Microradiographically, the relatively pure cystine calculi displayed a uniform density throughout the sections. There were some slight variations in density, but no intimate crystalline structure of the calculus could be seen.

Following decrystallization, the matrix material was seen to be almost entirely fibrillar in form, and was dispersed in a delicate network, without concentric laminations or recognizable regularities in structural characteristics. All of the fibrils were PAS-positive and metachromatic with toluidine blue. All fibrils contained a fine dispersion of aggregates of von Kossa-positive material, and the ash of the matrix contained approximately 40 % calcium (matrix content of the calculi varied between 3 and 10 % by weight).

Discussion

The following interpretative comments are consistent with the preceding observations.

Of the large numbers of renal calculi examined in the course of this and preceding studies, none has been found to be without an accompanying

organic matrix, which appears chemically to be essentially the same for all (7). This material apparently originates from the transitional epithelium (5). Conversely, a number of poorly crystallized 'soft stones' have been seen (4), especially in patients with a prior history of repeated stone formation, who were subsisting on a low calcium, low vitamin D, high phytate diet. It thus appears that the matrix material serves an architectonic function and is in fact a prerequisite to concrement crystallization.

As has been previously indicated (5), the matrix material is in two physical forms, amorphous and fibrous. Apatite has a peculiar and marked affinity for the fibrous component of matrix, analogous to that for the collagen fibrils in bone matrix. The fibrous matrix is organized and arranged in concentric laminations, with the microscopic aggregates of hydroxylapatite closely adherent to the fibrils. Hydroxylapatite is the most radiopaque material encountered in sections of renal calculi (8). Consequently the concentric laminations exhibit the greatest density in microradiograms. They also give the most marked reaction by the von Kossa method after gross decrystallization since these matrix-bound crystals are least readily removed by the chelating agent. The inter-laminar spaces are filled by crystals other than apatite, and by the amorphous portion of the matrix, which surrounds them.

As these secondary, interstitial (and, in a sense, incidental) crystals increase in size the uniformity of the laminations is accordingly altered. The degree of alteration corresponds to the size characteristically attained by the respective kinds of inter-laminar crystals, being least for uric acid and apatite stones, and progressively increasing in the following order: calcium oxalate monohydrate, magnesium ammonium phosphate, calcium oxalate dihydrate, and cystine. Indeed, in cystine stones the crystals become so large that all regularity of matrix structure is destroyed and only the resultant network of filamentous matrix remains. Presumably, the composition of the inter-laminar crystals is primarily determined by the ambient conditions during crystallization. If these conditions remain constant, the stone is 'pure', if not, it is 'mixed'. Whatever concentricity of apatite-covered lamination survives this phase of stone formation will be microradiographically obvious in the undecrystallized stone only if the interlaminar crystals are radiolucent (*e. g.* uric acid) or poorly radiopaque (*e. g.* magnesium ammonium phosphate). The laminations are obscured in undecrystallized stone having radiopaque crystals in the interlaminar spaces (*e. g.* calcium oxalate). Axial striations of crystal deposition are always related to axial laminations of matrix. After decrystallization, the laminations persist and are made more apparent by staining the fibrous matrix. The von Kossa procedure demonstrates the tenaciously held residual basic calcium phosphate crystals on these fibers. Metachromasia,

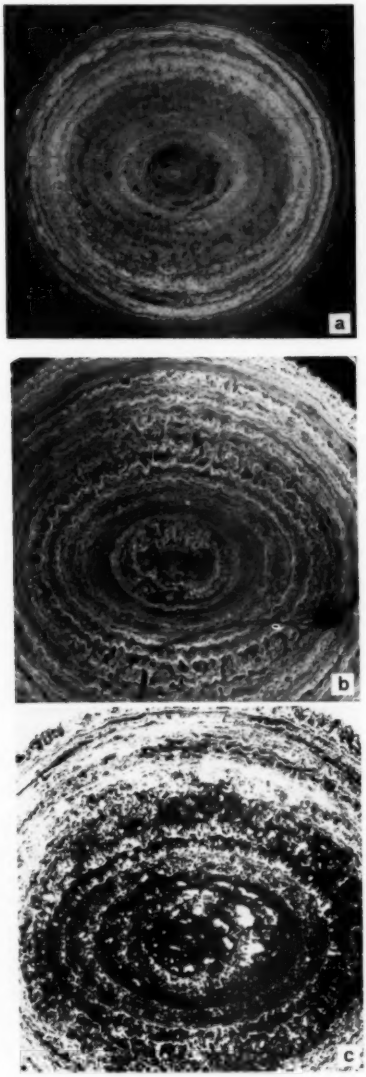


Fig. 11

Calcium oxalate, magnesium ammonium phosphate and calcium phosphate calculus from bladder.
Original size 52 × 47 mm.

a) Photograph of center section of original calculus.

b) Microradiogram of (a).

c) Photograph of matrix from section immediately adjacent to (b) after decrystallization. (Contiguous section utilized because the specimen was broken during microradiography.)

when present in decrystallized calculi, is generally in the laminar region and coincides with the areas of apatite deposition.

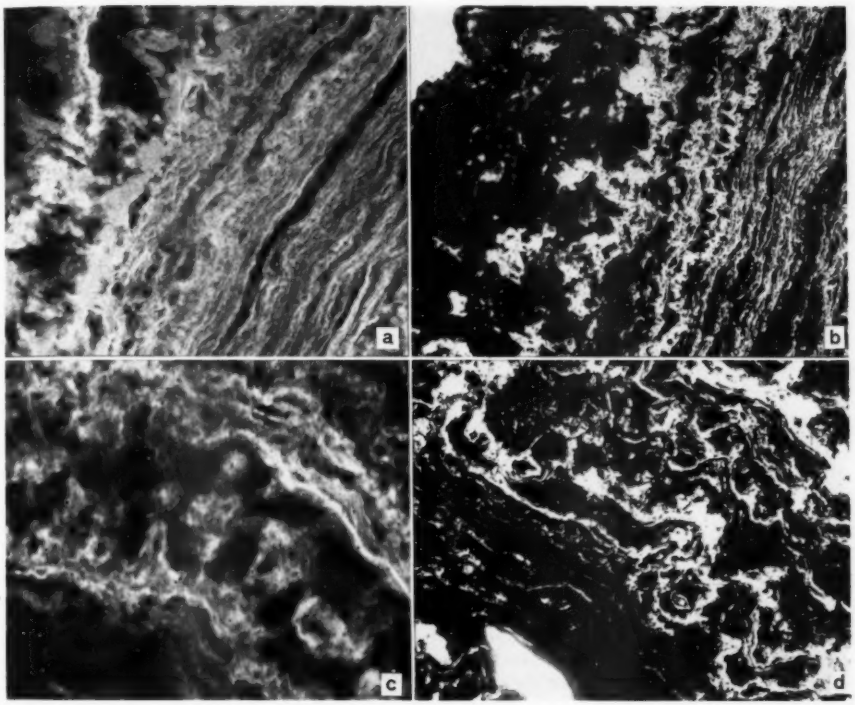


Fig. 12

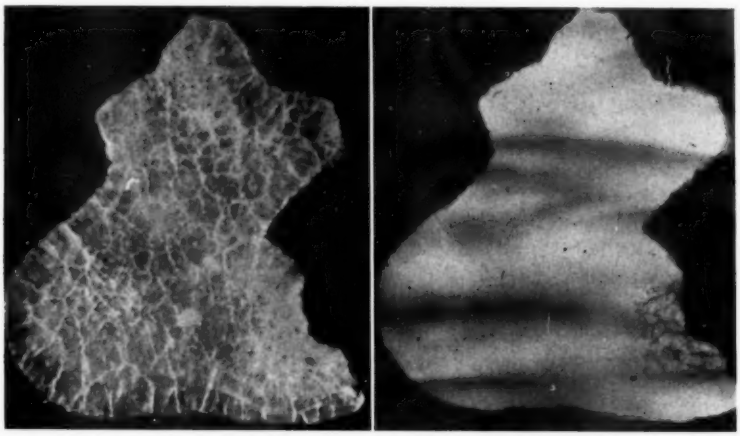
a) Marginal microradiogram of fig. 11 a. Large calcium oxalate dihydrate crystals form the surface with a thin basal layer of highly roentgen opaque calcium phosphate. Mixture of magnesium ammonium phosphate and calcium oxalate monohydrate forms the underlying body of the calculus.

b) Photograph of matrix of (a) after decrystallization, toluidine blue stain. 'Faults' in crystal deposition are filled with amorphous matrix which also contains much magnesium ammonium phosphate.

c) Microradiogram near center of (a). Crystals are a mixture of calcium oxalate monohydrate and magnesium ammonium phosphate. Fine lines of maximal density are apatite which is present in only a few areas.

d) Matrix of (c) following decrystallization, toluidine blue stain. Much amorphous matrix which contained magnesium ammonium phosphate. Calcium oxalate monohydrate occupied spaces between matrix. Apatite when present was supported by a narrow but very dense lamination of matrix and this was metachromatic with toluidine blue.

Thus, the matrix appears to be a prerequisite to the growth of stones and in addition may influence, or be influenced by, crystal formation to limit the size and shape of stones. Many forces may combine to mold matrix during the plastic stages: by compression (*e. g.* adjacent calculi,



a b

Fig. 13. Cystine calculus from kidney, original size 20 × 21 mm.

a) Photograph of center section of original specimen.

b) Microradiogram of (a) illustrates lack of detail of crystalline structure obtained by this method. Matrix is diffusely present as a fine filamentous network which disperses unless supported by a film of permeable collodion applied prior to decrystallization. The matrix gives a positive periodate Schiff leucofuchsin (PAS) reaction and is often metachromatic with toluidine blue. Matrix is not shown since the collodion binds both of these histochemical reagents and precludes clear reproduction by photography.

urinary passages, intermolecular attraction forces) or expansion (*e. g.* mechanical buckling, osmotic forces across membranes of matrix, crystal growth, and repulsive forces of oriented molecules). The influence of matrix on crystal deposition may be:

1) Calcium binding, ion-exchange, or epitactic stimulation of crystal (apatite) formation;

2) Creation of a favorable environment for crystallization between semipermeable layers of matrix (oxalate, triple phosphate, uric acid).

Conclusions

A comparison of the crystalline and matrix structures suggested that the size, shape, laminations, radial striations, and color of calculi are primarily determined by the mucoprotein matrix. This matrix is formed by aggregation and molecular orientation of uromucoid, a carbohydrate-protein conjugate produced by the transitional epithelium. The mechanism of this molecular orientation is unknown but is intimately associated

with the binding of calcium, phosphate, and water (hydroxyl) ions. This is the initial phase in all calculus formation. As the molecular orientation proceeds the amorphous gel tends to assume a perfectly spherical shape with regularly spaced laminations formed by the most closely aligned molecules of uromucoid. These laminations with their spatially arranged calcium, phosphate and hydroxyl ions act as epitactic stimuli to basic calcium phosphate (apatite) crystallization. Condensation of these laminations into semipermeable membranes provides a favorable environment for secondary crystallization. The composition of these inter-laminar crystals is primarily determined by the ambient conditions prevailing in the urine. As these interstitial crystals increase in size and number there is a commensurate alteration of the uniformity of the laminations. Masses of interlaminar amorphous uromucoid may block crystallization and thus produce 'faults' in the orderly arrangement of crystals. Many extrinsic or compression forces combine with intrinsic or expansion forces to produce the final shape of the fully crystallized calculus. The organic matrix is thus a prerequisite to concrement formation and crystal deposition is a secondary phenomenon.

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SUMMARY

Urinary calculi typifying the commonly encountered types of crystalline composition have been serially sectioned. Representative sections were mounted on plastic plates and polished to microscopic thinness. Crystalline structure of the sections was studied by microradiography utilizing high resolution plates. The sections were then decrystallized by diffusion of chelating agents into the specimens. The residual organic matrix was studied by histochemical techniques.

ZUSAMMENFASSUNG

Harnsteine, welche die üblichen Typen der kristallinischen Zusammensetzung exemplifiieren, sind mit Hilfe von Serienschnitten untersucht worden. Repräsentative Schnitte sind auf Plastplatten montiert und mikroskopisch dünn geschliffen worden. Kristallstrukturen derartiger Schnitte wurden mit der Mikroradiographie unter Benutzung photographischer Platten mit grossem Auflösungsvermögen studiert. Die Schnitte wurden dann durch Diffusion gelatinierender Mittel in die Präparate dekristallisiert. Die restierende organische Matrix wurde mit histochemischer Technik studiert.

RÉSUMÉ

Des calculs urinaires représentant les types fréquents de composition cristalline ont été coupés en série. Des coupes représentatives ont été montées sur des plaques de plastique et ont été polies jusqu'à une épaisseur microscopique. Leur structure cristalline a été étudiée par microradiographie au moyen de plaques à haute définition. Les coupes ont ensuite été décristallisées par diffusion d'agents chélateurs dans les préparations. La matrice organique résiduelle a été étudiée par les techniques histochimiques.

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FROM THE BIOLOGY OPERATION, HANFORD LABORATORIES, GENERAL ELECTRIC COMPANY, RICHLAND, AND THE ATOMIC ENERGY COMMISSION (CONTRACT W-31 ENG-52), WASHINGTON, U. S. A.

AUTORADIOGRAPHIC ANALYSIS OF PLUTONIUM DEPOSITION IN HUMAN SKIN

by

N. L. Dockum and *A. C. Case*

A human skin biopsy known to contain a quantity of plutonium was submitted for autoradiographic analysis. This report describes the autoradiographic technique employed to locate the site of deposition and the quantity of plutonium found in the area by radioanalysis of the skin biopsy.

Methods

The human skin biopsy, 1 cm long, was fixed in Bouin's solution, dehydrated in 'Cellosolve', cleared in benzene, and embedded in paraffin.

Sections were cut at 8 microns and a radiochemical analysis of a number of the sections was made to determine autoradiographic exposure time. Individual sections contained from 0 to 362 disintegrations per minute. Initial exposures were made for 19 $^1/_2$ hours and later exposures were made for 4 hours. The film type utilized was NTA, 5 micron (Nuclear Track, Alpha) with a 1 micron 'T'-coat to prevent abrasions of the emulsion. The autoradiograms were developed for 10 minutes in D—19 at 18° C, washed, and fixed in

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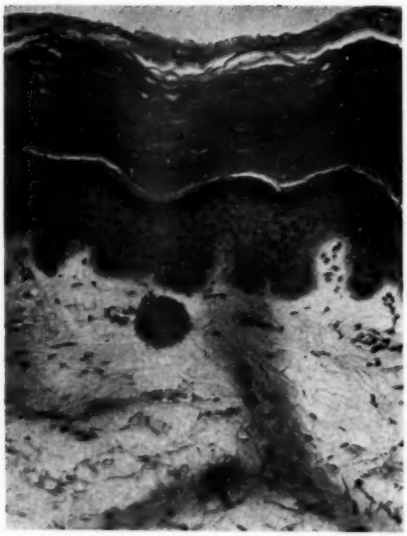

Fig. 1. Autoradiogram of human skin showing 'star' formation of alpha tracks immediately beneath the epidermis. Hematoxylin and eosin preparation. Enlargement × 175.

Kodak acid fixer. The autoradiograms were then stained with hematoxylin and eosin (DOCKUM et coll. 1957).

The counting procedure for the specimen consisted of scanning, under a microthin window alpha detector, approximately 250 individual sections. Of the more radioactive sections, 33 were saved for autoradiography. Eighteen of these were individually ashed and their activities determined in alpha proportional flow counters. Counts obtained from ashed samples were considered more accurate than those obtained directly from paraffin sections. The ratio of the two sets of counts was then used to correct counts obtained from all the individual sections that were used for autoradiography. All of the remaining sections were consolidated, ashed, and their activity determined by radioanalysis.

Results

An analysis of the autoradiograms prepared showed that the plutonium was deposited immediately below the epidermis (Fig. 1) and at points that were from 700 to 900 microns below the *stratum corneum* (Figs. 2 and 3).

Aggregates of the alpha emitting particles were scattered throughout the tissue sections. Two major sites of deposition were separated by approximately 1,700 microns. The contamination appeared to be particulate rather than diffuse and the single particles gave rise to a 'star' effect, as evidenced by the track formation.

No contamination was observed on the outer surface of the *stratum corneum* in those sections of which autoradiograms were made. Random tracks were observed in the epidermis in some areas.

An initial survey of the specimen with a Scintillation Poppy was negative. The total activity for the entire specimen determined by radioanalysis was 0.0046 μC.

The International Commission on Radiological Protection recommends that the total body limit should not exceed 0.04 μC.

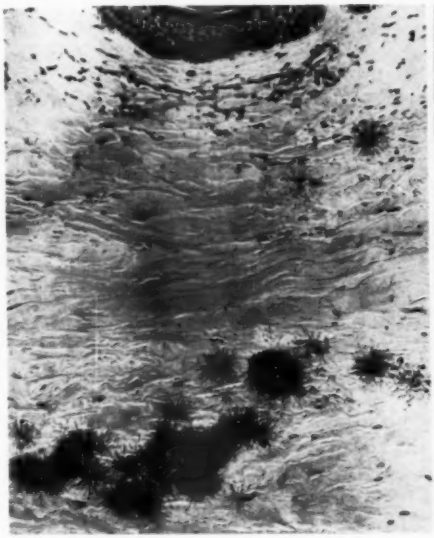

Fig. 2. Autoradiogram of human skin showing distribution of plutonium and alpha tracks approximately 800 microns beneath *stratum corneum*. Hematoxylin and eosin preparation. Enlargement × 175.

Fig. 3. Autoradiogram of human skin showing distribution of diffuse and particulate plutonium with resultant alpha track distribution. Hematoxylin and eosin preparation. Enlargement × 175.

Acknowledgements

The assistance of the Radiochemistry Laboratory and Mrs. Glenda Vogt of the Microscopy Group is gratefully acknowledged.

SUMMARY

Autoradiography is recommended as a routine procedure to supplement information gained from chemical analysis and counting procedures in human skin plutonium contamination incidents where biopsies are taken.

ZUSAMMENFASSUNG

Die Autoradiographie als Routinmethode wird zur Vervollständigung der nach chemischen Analysen und Messprozeduren erhaltenen Information in den Fällen von Plutoniumkontamination der menschlichen Haut empfohlen, in welchen Biopsien gemacht worden sind.

RÉSUMÉ

Les auteurs recommandent l'autoradiographie comme méthode usuelle pour compléter les renseignements fournis par l'analyse chimique et par les méthodes de comptage appliquées aux incidents de contamination de la peau humaine par le plutonium, dans les cas où on a prélevé des biopsies.

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FROM THE CANCER RESEARCH LABORATORIES, MEHARRY MEDICAL COLLEGE, DEPARTMENT OF RADIOLOGY AND RADIOISOTOPE UNIT, VETERANS ADMINISTRATION HOSPITAL, NASHVILLE, TENNESSEE, U. S. A.

INTRAVENOUS RADIOACTIVE GOLD IN THE TREATMENT OF CHRONIC LEUKEMIA

Comparison of results with conventional roentgen therapy to the splenic area

by

P. F. Hahn, D. G. Lareau, B. L. Feaster, E. L. Carothers, F. Gollan, G. R. Meneely, and *D. Sherman*

On several occasions we have reported on the successful use of radioactive colloids administered intravenously in the treatment of chronic leukemias (3) (7) (1) (2). We used radio-gold when it first became available in the fall of 1946 as a reactor produced substitute for Mn $^{54}O_2$ colloids which we had developed for such therapy. In the interim we have treated approximately 80 such cases. Several years ago it was decided to alternate therapy with intravenous gold and conventional roentgen irradiation to the spleen in order better to evaluate the comparative efficacies of these two forms of treatment. This has been done in 17 patients. The comparative results obtained by these two methods are described below.

The patients were all male veterans, most of them non-residents, and therefore frequently it was impossible to control complete management of the patient. For example, in a number of instances the treatment was complicated by the administration of whole blood, cortisone,

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or other therapeutic agents. However, there are a sufficient number of uncomplicated remissions to allow an evaluation of the procedures. In one case six alternating roentgen and Au^{198} induced remissions were studied. The selection of patients was essentially random. The patients varied to a considerable degree as to the stage of the disease process as well as in age. Both of these factors are important in evaluating the results of therapy since the degree and duration of remissions are markedly affected by each.

We have found that usually the administration of Au^{198} colloids intravenously is followed by periods of satisfactory remission lasting from 4 to 6 months on the average and sometimes as long as $1^1/_2$ years in older subjects where the disease usually runs a more benign course. In one patient described below we encountered a remission of $2^1/_2$ years when the dose was doubled.

We shall present the protocols of two patients who reflect the use of these two modalities of radiation, external and internal, in the treatment of leukemia. It might be said here that the clinical results obtained were essentially the same in all 17 cases using both forms of treatment. The chief advantage found in the use of intravenous gold colloid therapy resided in its being a single treatment type of therapy given to an ambulant patient and therefore applicable to out-patient therapy and secondly to the considerably lowered frequency of nausea and anorexia and other post-irradiation symptoms as compared to roentgen treatment.

Earlier we stated that our dosage of radio-gold varied from 0.8 to 1.2 mC/kg of body weight. More recently we have tended to use a standard dose of approximately 50 mC for the initial administration of the gold colloid, of course taking into consideration any marked variations in size of the patient and reducing or increasing somewhat the dosage accordingly. This dosage has been found to produce a remission in practically all except terminal cases. The leukocyte level is usually found to be reduced to normal or near normal limits. The differential blood studies generally show a disappearance of the myelocytic forms in the peripheral circulation in the myelogenous leukemias and a marked decrease or disappearance of the blast and smudge forms in lymphogenous leukemia. Without transfusion in the early cases the hemoglobin level rises to or approaches normal. As the number of treatments by either method increases, the response of splenomegaly is diminished until the condition ultimately usually becomes refractory to further therapy.

Methods

The radioactive gold colloid used was processed by the method as originally developed by us. (Obtainable in calibrated, sterile and pyrogen-free form ready for administration from Abbott Laboratories, Oak Ridge, Tennessee.) Administration was usually accom-

plished by the direct shielded syringe technique. The operator carries out a venipuncture while the radio-biologist simultaneously removes the required amount of material from the bacterin vial. The latter procedure is carried out by first barely puncturing the rubber stopper of the upright vial with a needle and syringe. The syringe is detached in order that pressure equilibration may be attained. An amount of air corresponding to the amount of colloid to be removed is drawn into the syringe which is re-attached and the air injected into the vial. The latter with its lead container is inverted and the colloid withdrawn. When the operator has indicated that he has free flow of blood the syringes are exchanged and injection is made immediately requiring only a few seconds. The syringe is flushed with blood from the patient. All contaminated equipment is placed in escrow for a period of two weeks before cleaning with *aqua regia* prior to further use. Monitoring badges, when worn on the chest, used with the direct shielded syringe technique have indicated a maximum of 30 mr exposure. On some more recent occasions the "wash-over" technique was used which minimizes the exposure of the operator.

Case reports

Case 1. White male civil engineer, was completely well and energetic until 8 months prior to his first admission at which time he began to have progressive weakness and loss of energy.

During the 4 months before admission to Thayer VAH on May 14th 1951 he had lost 4.5 kg in weight. Two months earlier he had had influenza associated with jaundice. At that time he noticed a mass in the left upper quadrant, dizziness and weakness, the latter so marked as to make him bedridden. There were no bleeding tendencies. The temperature was normal. The spleen extended to the umbilicus medially about 13 cm below the left costal margin and to the mid-line. It was smooth, hard and slightly tender. There was no generalized lymphadenopathy. In spite of the high white blood cell count (RBC 4.22, WBC 239,000) there was no marked anemia. About a week later, a bone marrow aspiration showed chronic myelogenous leukemia. He was treated with 50 mC of radioactive colloidal gold intravenously. During the following 2 weeks the leukocyte count approached normal levels and there was a marked drop in the percentage of myelocytes. The spleen decreased to 9 cm in the dimensions mentioned above and there was considerable subjective improvement with no symptoms of nausea or anorexia. Discharged on June 6th (RBC 4.32, WBC 48,650).

Readmitted 1 month later. During the interim his strength had increased as well at his appetite. There had been no nausea, vomiting, bleeding or pressure symptoms. As time of admission there was no significant adenopathy. The spleen was firm, discrete and palpable 6 cm below the left costal margin. There were sizable ecchymoses on the inner aspect of the right calf. Hematological findings were within normal limits except for a relatively high hematocrit value of 54 %.

The patient was seen again on August 15th at which time there was a beginning relapse as evidenced by the white blood cell count (60,000). He was not treated, however. On readmission on September 17th he stated that he had been working 10 hours a day. However, he presently had cough and some pain in the right upper quadrant. Examination showed a fine papular eruption in the upper abdomen. There was one anterior cervical node and also one in the left axilla. The spleen was down 6 cm but the liver was not palpable. The blood studies showed an extensive degree of relapse (RBC 5.00, WBC 219,500) and from September 25th to October 3rd 1951 roentgen therapy was administered. An air dose of 2,400 roentgens was given over the spleen through 4 ports. As therapy proceeded the patient felt well and the spleen decreased in size until it was barely palpable at the edge of the costal margin. He was discharged on October 10th 1951.

Readmitted on January 16th 1952 the patient stated he had felt fairly well in the interim. During the past two weeks he had had return of weakness and malaise. On examination no palpable lymph nodes were present nor was the liver felt. The spleen was 10 cm below the left costal margin in the midline. Hematological studies showed a polycythemic erythrocyte picture and leukocyte findings of relapse (RBC 5.86, WBC 169,000). 45 mC of gold colloid were given intravenously on January 23rd and 5 days later the patient stated that he felt better. A week after treatment, there was a beginning improvement in the blood picture which had not had sufficient time to approach normal values at time of discharge.

He was readmitted on May 12th with the chief complaint of recurrent weakness. He had worked 10 hours daily in the interim until 2 weeks before admission. Patient was scheduled to receive roentgen on this admission according to plan but having had considerable radiation sickness after last roentgen therapy stated that he preferred gold. The decision of the Tumor Board, however, was to adhere to the plan and consequently an air dose of 1,800 r was delivered over the spleen through 3 ports. Following treatment the patient felt stronger although he complained of nausea. The hematologic picture resumed a normal configuration. Discharged on May 28th (WBC 13,100).

He was readmitted on September 22nd. There had been no nausea or vomiting but 10 weeks prior to admission patient had mild diarrhoea and some severe burning epigastric pain. The spleen was down to the iliac crest extending beyond the mid-line. The liver was down 3 cm in the mid-costal line. No adenopathy or hemorrhagic manifestations were noted. Hematologically there was a picture of moderate relapse with still no anemia (RBC 5.36, WBC 142,000). 75 mC of gold were given intravenously and a week later the patient was discharged having had no unfavourable reactions.

He was readmitted on January 12th 1953. The white count had dropped to 5,000 to 10,000 in the interim but the counts were now on admission 125,500 and 3.84. However the spleen did not shrink to any considerable degree as it had done previously. Patient had been running low grade fever at home daily, but he had felt well until 3 weeks previously when fever increased and his spleen started to enlarge. The spleen was found to be hard, extending into the pelvis 2 cm beyond the mid-line. The liver was smooth, nontender, extending 3 cm down. There were no hemorrhagic phenomena and no peripheral adenopathy. Another series of roentgen treatments was begun and a total air dose of 2,400 r was given in 9 days through 3 ports. There was marked remission of symptoms afterwards. Discharged on January 26th (WBC 5,600).

Readmission on March 9th with a chief complaint of fever, left pleuritic chest pain and general weakness. After the last two treatments (1 gold and 1 roentgen) the spleen had not responded satisfactorily and the patient had not had as complete a remission of fever and weakness as after previous treatments. On returning home patient felt poorly and became acutely ill three weeks prior to admission at which time he developed increasing malaise, myalgia, high fever and night sweats. There was a cough but no hemoptysis. The liver was down 3 to 4 cm and was smooth, firm and non-tender. A hard spleen, moderately tender, extended into the pelvis 3 cm beyond the mid-line. On a hematological basis the patient was in a moderate state of relapse, finally showing anemia. 50 mC of gold were administered intravenously. The patient before and following therapy had high spiking fever daily rising to between 40 and 40.5° C.

He developed acute pain over the spleen about March 17th 1953 (RBC 3.91, WBC 83,000). On that day there having been no immediate response to gold therapy, roentgen was administered to the spleen amounting to 1,500 r air dose in 5 days. He showed slight subjective improvement for a few days but developed a shocklike picture which suggested hemorrhage into various viscera. He died on March 23rd 1953. The diagnosis at autopsy was: Chronic myelogenous leukemia, coronary arteriosclerosis, aortic arteriosclerosis, atrophic gastritis, and testicular atrophy.

In the treatment of this patient, the plan of alternated types of therapy was adhered to. His clinical course and response to therapy were quite typical of patients with chronic myelogenous leukemia with the exception that the erythrocytic components exhibited a polycythemic rather than an anemic picture until the terminal stage. Response to gold and roentgen according to accepted therapeutic criteria seemed to be about equally as good for one as for the other. There was a lower degree of radiation sickness phenomenon following the gold and because of this the patient stated on several occasions that he preferred this type of therapy. As is commonly encountered in both types of therapy the spleen responded initially in a satisfactory manner but after several treatments became relatively refractory.

The length of life from time of first symptoms was about 3.5 years. This is the average life-span found by investigators using a wide variety of methods of treatment. With a few exceptions no claims seem to have been made by most clinicians for any particular drug regarding any increased life-span following therapy. Until a more satisfactory agent is made available it would seem that our chief aim should be to maintain leucocyte levels within safe limits to avoid thrombotic accidents and achieve as much palliation as possible with a minimum of discomfort to the patient.

Case 2. A 65-year-old male negro farmer, was first admitted to the Nashville Veterans Administration Hospital on June 21st 1949 with a chief complaint of hemorrhoids. Upon routine examination it was found that the leucocyte level was 35,000 and study of the sternal bone marrow showed typical increases in the granulocytic series and a relative increase in young forms compatible with early chronic myelogenous leukemia. No focus of malignancy was elicited which might be a basis for a leukemoid reaction. Since he had no symptoms he was discharged without treatment.

Upon readmission on July 16th 1952 with a chief complaint of pain and swelling in the right shoulder of 3 weeks duration a systolic murmur was noted. The liver was down 3 cm and was tender. There was a large tender very firm swelling underlying the trapezius on the right and extending into the shoulder and down under the spine of the scapula. The nodes in the inguinal and axillary regions were enlarged. Marked leukocytosis and anemia were present (RBC 1.98, WBC 347,000). 100 mC of radioactive gold colloid were administered intravenously as were also 1.5 litres of blood. In spite of this large dosage of gold there were no untoward symptoms in the ensuing several weeks during which period the leukocyte level dropped to but not appreciably below normal levels with a return of the differential white cell series to relatively normal levels. However, there was a disappearance of myelocytes from the circulation and a lymphopenia. The platelets were normal in number upon discharge on August 11th 1952. At this time the spleen was reduced to approximately half the size of that on admission.

On February 28th 1955 a note from the patient's physician stated that he had not been treated since the gold had been administered until $2^1/_2$ years later. At that time his liver was slightly palpable and the spleen extended into the pelvis.

He was readmitted to the hospital on March 25th 1955 because of leukocytosis (RBC 2.32, WBC 500,000) and still chief complaint of hemorrhoids. The spleen was markedly enlarged and he had had a few episodes of shortness of breath. The liver was

down 6 cm below the right costal margin. The spleen was enlarged to within a few cm of the pubis and its right margin extended to the mid-line. There were no appreciable nodes. A chest roentgen examination showed changes which were consistent with lymphatic infiltration of both lung fields. Bone aspirations showed a typical picture of chronic myelogenous leukemia. Three transfusions of 500 ml each were given.

Fifty mC of gold were administered intravenously on April 12th resulting in no complaints of nausea during the ensuing week (WBC 440,000). Ten days following the treatment the patient stated that he felt much better and it was found that the spleen had diminished in size quite appreciably. One month following this therapy the white blood cell level had only dropped to 43,000 and the peripheral blood showed presence of some blast forms and myelocytes. Following hemorrhoidectomy the patient was discharged. Upon return one month later in a moderate state of hematologic relapse roentgen therapy was directed to the spleen in the course of 10 treatments over a 17 day period. He expired on last day of therapy, June 30th 1955.

This patient is presented not so much for the comparison of the results of radioactive gold therapy with roentgen as from a standpoint of dosage of intravenous gold. A double dose was administered at time of first treatment and therefore the patient was watched carefully during the next several weeks for signs of leukopenia, anemia or bleeding tendencies. None of these phenomena occurred and neither did the patient show signs of anorexia or nausea. The leukocyte level dropped to within normal limits. The erythrocyte picture improved considerably but this might be ascribed to 3 transfusions under these circumstances in spite of the fact that we have noted such improvement in other patients without recourse to transfusion. The most striking feature was the prolonged remission of $2^1/_2$ years obtained following the administration of 100 mC of radio-gold. On subsequent admission our usual dose of 50 mC of gold did not succeed in reducing the leukocyte level to normal levels. Administration of such latter dosages of gold are usually accompanied by a complete remission lasting from 4 to 6 months (1) (2). When first using this modality of therapy we had undertreated a number of patients and in spite of this had still obtained remissions in a few with dosages as low as 10 mC intravenously (1).

Discussion

Following intravenous administration we have shown that approximately 90 % of the colloid is resident in the liver within 15 to 20 minutes after injection (8). In the average-sized individual the administration of such a 50 mC dose will therefore result in about 2,000 to 2,500 equivalent beta roentgens delivered to this organ throughout the decay of the isotope (6). This amount is well tolerated as shown by repeated negative cephalin flocculation tests as well as lack of leukopenia in such treated patients. Parenthetically, it might be stated that we have repeatedly shown that it requires delivery of upward of 50,000 equivalent beta roentgens to the

liver in experimental dogs to produce irreversible pathological changes in the organ (4) (5).

The hematologic response to such therapy can be fairly satisfactorily assessed. The evaluation as regards reduction of lymphadenopathy and particularly splenomegaly and hepatomegaly leaves much to be desired. Although in the case reports presented here we have adhered to such conventional practice we feel that it means relatively little to state that a given organ by palpation is so many centimetres below the costal margin or to the left or right of the umbilicus, near the pelvic brim or that it fills such and such a fraction of the abdominal cavity. Such irregularly shaped organs as the liver and spleen do not lend themselves readily to estimation of size by present clinical methods. Such quantitative attempts must therefore, for the time being, be looked upon largely as guess work. However, other signs such as relief of anorexia, weight gain (with due recognition of edema or ascites if present), sense of well being, reduction of weakness and fatigue, etc. must all be taken into consideration in the evaluation of the therapeutic response in leukemia and neither are they subject to ready quantitative assessment.

The tremendous degree of variation in individuals in their response to the disease and to therapeutic efforts makes the leukemic patient a difficult one to evaluate and certainly one in which it is not easy to express in tabular form the results of therapy. Judgement is bound to play a considerable role in evaluation of the results obtained and it is therefore likely prejudice may be involved. We have seen little indication that would suggest that with either intravenous radioactive gold colloids or roentgen therapy the life-span of the chronic leukemic patient is appreciably increased in spite of the fact that the patient is able to resume a relatively normal life during remissions. Others have claimed such increase in life-span using P^{32} although some selection of patients cannot be excluded.

In the second patient recorded, the first large intravenous dose of gold resulted in an excellent remission with no adverse reactions. It suggests that perhaps we might try higher intravenous doses of gold as a rule in the management of chronic leukemias.

SUMMARY

In 17 patients the use of intravenously administered radioactive colloidal gold and that of conventional roentgen therapy to the spleen was alternated in patients with chronic lymphogenous and myelogenous leukemia. The clinical results of treatment by both methods were essentially the same. Remissions lasting from 3 to 6 months were the rule. The chief advantages encountered in the use of gold therapy resided in its being a single injection form of therapy to the ambulant patient, thus providing economy of time and money. Furthermore, the incidence of phenomena associated with radiation effects such as anorexia and nausea were decidedly less frequently found in the gold treated patient.

Normally about 50 mC of colloidal gold was administered initially. It is suggested that further studies at higher levels of therapy should be made in order to corroborate the results obtained in one case.

ZUSAMMENFASSUNG

Siebzehn Patienten mit chronischer lymphatischer und chronischer myeloischer Leukämie wurden alternierend mit intravenöser Injektion von kolloidalem Radiogold und mit konventioneller Röntgenbestrahlung der Milz behandelt. Die klinischen Behandlungsresultate mit beiden Methoden waren im wesentlichen gleichartig. Remissionen von 3 bis 6 Monaten waren die Regel. Die Hauptvorteile der Goldtherapie bestehen darin, dass der ambulante Patient nur eine Injektion erhält und so Zeit und Geld gespart wird, und dass mit der Strahlenwirkung verknüpfte Phänomene wie Übelkeit und Erbrechen wesentlich weniger häufig bei den mit Radiogold behandelten Patienten auftreten. Gewöhnlich wurden initial 50 mC kolloidales Gold gegeben. Es wird betont, dass weitere Studien mit grösseren Therapiedosen gemacht werden sollten, um die in einem Falle gewonnenen Resultate zu bestätigen.

RÉSUMÉ

Chez 17 malades atteints de leucose chronique lymphoïde ou myéloïde on a utilisé alternativement l'or radioactif colloïdal par voie intraveineuse et la roentgenthérapie splénique habituelle. Les résultats cliniques de ces deux méthodes de traitement ont été identiques. Les rémissions de 3 à 6 mois ont été la règle. Le principal avantage de l'emploi de l'or est qu'il constitue un traitement ambulatoire par une injection unique, réalisant ainsi une économie de temps et d'argent. De plus, la fréquence des troubles accompagnant les effets des radiations, tels que l'anorexie et les nausées, a été nettement moins grande chez les malades traités par l'or. On a normalement administré au début 50 mC d'or colloïdal. Les auteurs pensent qu'il faudrait continuer à étudier l'effet de traitement plus intense, de façon à corroborer les résultats qu'ils ont obtenus dans un cas.

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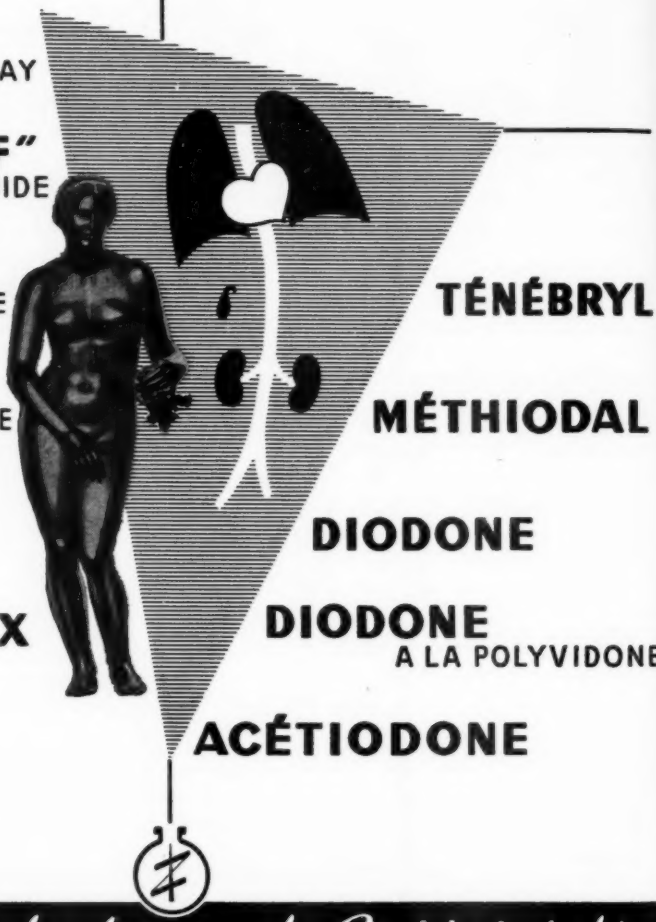

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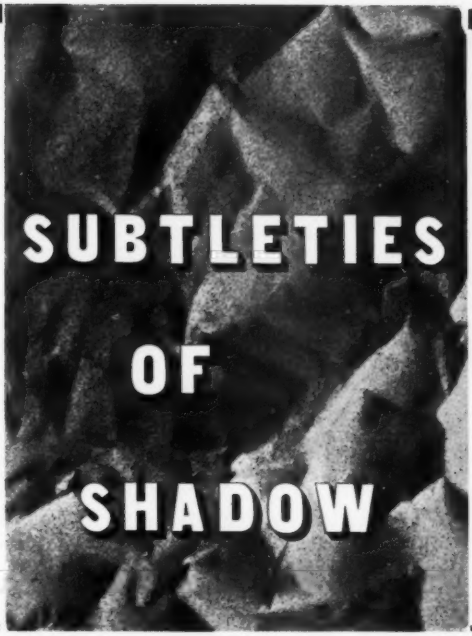

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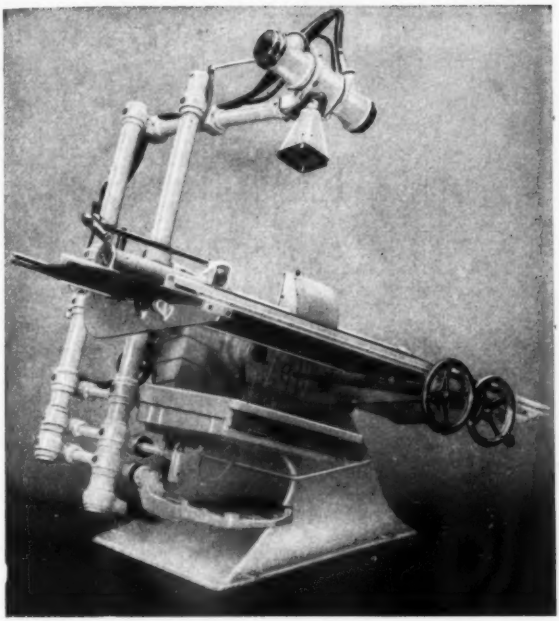

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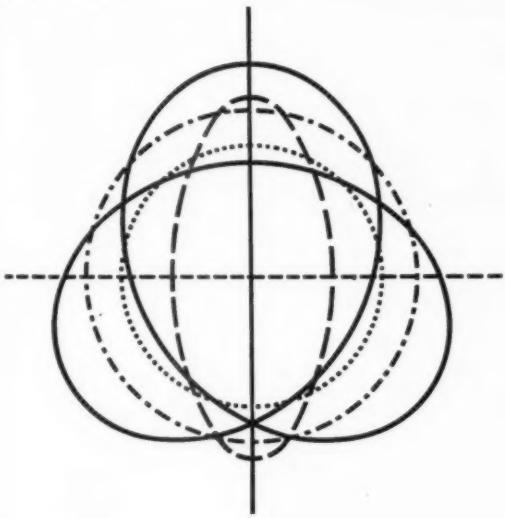

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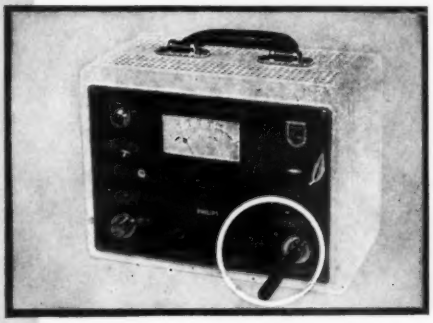

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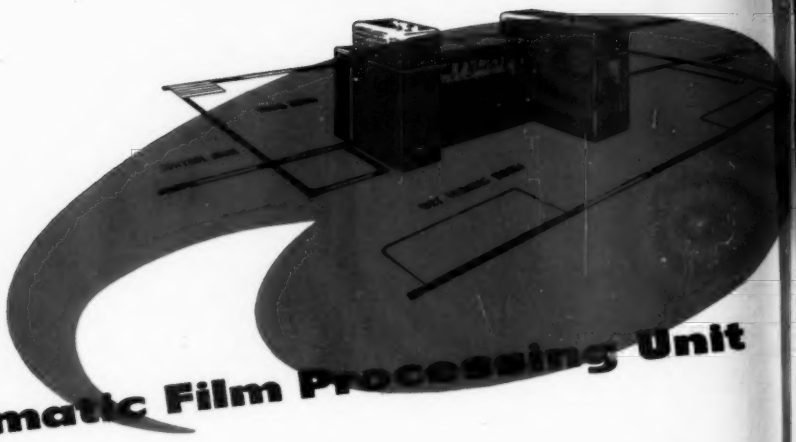

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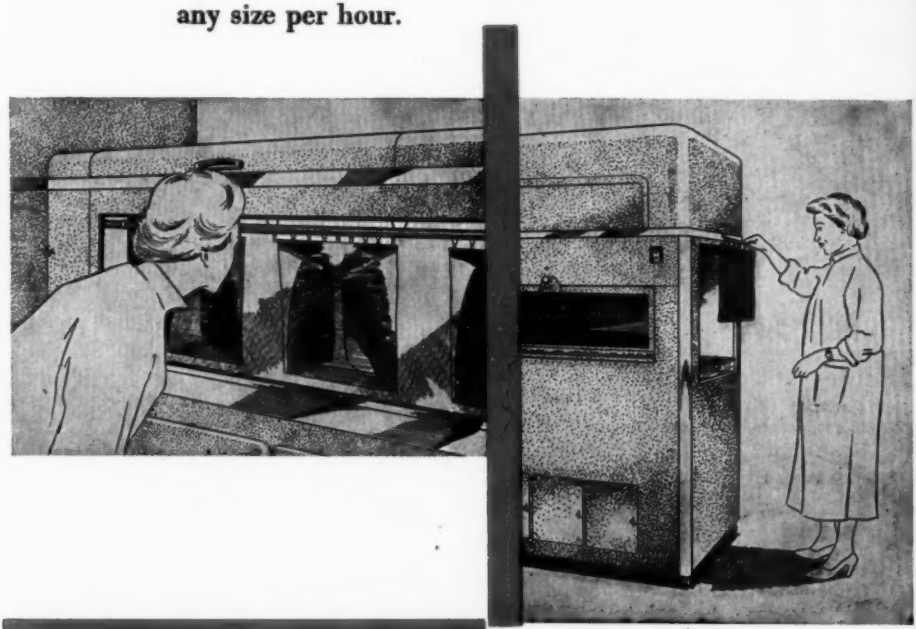

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